

A HANDBOOK OF TROPICAL THERAPEUTICS

BY

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TO
MAJOR-GENERAL D. P. GOIL
K.H.P., M.B., CH.B., F.R.C.S.E., I.M.S.
AS A TOKEN OF ESTEEM

PREFACE

Since 1921 I have been engaged in teaching post-graduate students at the Calcutta School of Tropical Medicine and nearly a hundred medical practitioners from all parts of India and some from other tropical countries have annually passed through my hands. Medicine is taught in the Medical Schools and Colleges of India, chiefly from British and American text-books where the climatic and the morbid conditions are somewhat different from those in the tropics. It is not surprising, therefore, that the therapeutic methods described therein are not universally applicable in the environment under which the medical practitioners work in the tropics. It is not unusual to meet with disappointment in results and even untoward effects from the applications of such methods.

The importance of this fact has impressed me so greatly that I have thought it worth while to review the whole subject of therapeutics with due regard to the climatic conditions met with in the tropics generally and in India particularly. All the experience gained during the last fifteen years of intimate association with post-graduate teaching and treatment of patients in a well-equipped research hospital such as the Carmichael Hospital for Tropical Diseases has been collected and put together in book form so that the information is readily available. To encourage the rational use of drugs, the pharmacological actions of various remedies have been described before their therapeutic uses are discussed. The ætiology and pathology of disease have been mentioned briefly only in so far as it is necessary to make the treatment more comprehensible. These additions have made the book somewhat bulky.

I would like to emphasize that not only does this book include the results of my own personal experience, but that of many of my colleagues and co-workers in the Calcutta School of Tropical Medicine, who have very generously helped me in producing this volume. Had it not been for this co-operation and help the task would have been an impossible one. Every

section of the book has thus been thoroughly scrutinised by various experts on particular subjects, who have liberally contributed valuable criticisms and suggestions, which have been incorporated. In this connection I would like to put on record my very great indebtedness, my sense of gratitude and appreciation for the help which has been ungrudgingly given me by everyone concerned. Capt. C. L. Pasricha, I.M.S., Professor of Pathology and Bacteriology, was good enough to revise large sections of the part dealing with bacterial and virus diseases, and the skin diseases portion was entirely written by Dr. K. P. Banerji, and revised by Dr. L. M. Ghosh, from the notes of the late Lieut.-Col. H. W. Acton, C.I.E., I.M.S., who was a pioneer in tropical dermatology and who has greatly added to our knowledge of skin diseases in the tropics by his researches financed entirely by the Indian Research Fund Association. Dr. L. E. Napier and Dr. P. A. Maplestone, D.S.O., not only overhauled the sections dealing with their own subjects but went through the galley proofs and page proofs which involved an enormous amount of labour. To Dr. K. V. Krishnan, I am obliged for his help in writing the section on the Reticulo-endothelial system, and to Drs. J. P. Bose and Dharmendra for the sections on Diabetes and Asthma respectively. To Lt.-Col. R. Knowles, C.I.E., I.M.S., Professor of Protozoology, School of Tropical Medicine, Calcutta, Lt.-Col. J. Taylor, D.S.O., I.M.S., Director of the Central Research Institute, Kasauli, and Lt.-Col. E. H. Vere Hodge, I.M.S., Professor of Medicine, Medical College, Calcutta, I am grateful for criticisms and suggestions.

The book consists of six parts, as well as a dictionary of diseases and treatment, and appendices. Part I deals with general considerations in therapeutics and includes chapters on the action of drugs and conditions modifying drug action, modes of administration (including details of technique), chemotherapy (including drug resistance and the rôle of the reticulo-endothelial system), physiotherapy, diet and dietetics in the tropics, pyrexia, treatment of pain and insomnia and the use of tonics. This part may appear to be somewhat overloaded but the information given therein was considered to be essential. If

future editions are called for some of the sections from this part could perhaps be more appropriately transferred to the dictionary. Part II deals with the treatment of helminthic diseases and has been largely extracted from my book on this subject, written in conjunction with Dr. Asa C. Chandler, *Anthelmintics and their Uses in Medical and Veterinary Practice*, with the kind permission of the publishers, Messrs. Williams & Wilkins of Baltimore. A considerable amount of new information and the recent advances on the subject have been included. Part III deals with remedies used against protozoal diseases and is composed of four sections. The first section deals with remedies used against amœbiasis, the second against leishmaniasis and trypanosomiasis, the third against malaria and the fourth against spirochætal organisms. This is the most important part of the book from the point of view of tropical diseases and every effort has been made to discuss the relative value of different remedies in the treatment of protozoal diseases, as well as their modes of action, and to give a detailed account of the toxic effects produced and how to deal with them. Part IV discusses the treatment of bacterial and virus diseases which are of special interest in tropical climates. A large amount of space has been allotted to the general discussion on the uses of vaccines, sera and bacteriophage in therapeutics. Part V deals with the treatment of miscellaneous diseases met with in the tropics. The nutritional disorders, such as beriberi, epidemic dropsy, pellagra, etc., and metabolic disorders, including diabetes mellitus and obesity, have been dealt with. Special chapters have been given on tropical neurasthenia, treatment of the bites of snakes and other venomous animals and drug addiction. Every section up to here is followed by a list of the general literature and a selected bibliography which will be useful to those who want further details. Part VI deals with the treatment of skin diseases and is followed by a dictionary of diagnosis and treatment of the conditions met with in the tropics which cannot be strictly grouped under the heading of tropical diseases. The appendices give abstracts from journals, bringing certain sections up to date (end of 1935); there are also posological tables of drugs and preparations, notes regarding important non-official remedies, physiological

constants, tables of bacteria, metazoa and protozoa, and a large amount of other information required almost every day by the medical practitioner. The book is so designed that it will not only serve as a reference book for medical practitioners in the tropics but will also meet the requirements of senior students appearing in their final examinations. In spite of the great care that has been taken, the book possibly has many shortcomings and blemishes. I shall be very grateful for criticisms and suggestions so that in the next edition these defects can be removed.

I wish to acknowledge my indebtedness to the authors and publishers of the following books from which I have freely borrowed informations:—*A Manual of Pharmacology* by W. E. Dixon ; *A Manual of Pharmacology* by T. Sollmann ; *Parasitology* by Blacklock and Southwell ; *Tropical Medicine* by Rogers and Megaw ; *Recent Advances in Chemotherapy* by G. M. Findlay, and *Applied Pharmacology* by A. J. Clark.

I wish to place on record the valuable assistance I have received in writing this book from my former pupils and now co-workers in this institution, Drs. B. P. Mukherji, N. N. De, S. K. Ganguly and R. N. Chaudhuri who have worked incessantly, and M. D. Chakravartty on whom fell the task of abstracting from journals and looking up references. To Prof. S. Ghosh and Drs. J. C. Gupta, J. S. Chowhan, G. S. Chopra and B. Sen, I am very grateful for many valuable suggestions. The most difficult task of getting the book through the press has fallen on the shoulders of Dr. I. B. Bose who has worked ungrudgingly for over two years, sometimes under most difficult and trying circumstances.

To the Governing Body of the Indian Research Fund Association, Major-General C. A. Sprawson, C.I.E., K.H.P., I.M.S., Director-General, Indian Medical Service, and Col. A. J. H. Russell, C.B.E., K.H.P., I.M.S., I am very grateful for the generous grants they have given me to carry out researches in connection with indigenous drugs, drug addiction and the treatment of diseases in the tropics. But for the work done under the auspices of this Association the book would have lacked a good deal of originality.

To the publishers, the Art Press, I am very grateful for the efficient manner in which they have carried out the work. I am particularly grateful to Mr. N. Mukherjee, the proprietor, whom I cannot thank sufficiently for the patient and generous manner in which he has treated me.

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A HANDBOOK OF TROPICAL THERAPEUTICS

PART I

GENERAL CONSIDERATIONS IN THERAPY

CHAPTER I

ACTION OF DRUGS

The source and nature of drugs. From the remotest times man has looked for remedies to alleviate sufferings, the problem of cure of disease has faced mankind as far back as memory can take us and the evolution of drugs is traceable to the desire of man to overcome personal discomfort and disease. In course of time the knowledge of drugs and with it their number and uses have gradually increased. Although modern science has opened up new sources of remedies from the mineral resources and the animal kingdom, reliance is still placed to a great extent, upon plant life for the supply of drugs. The plants may occur in nature or they may be cultivated; they are collected and active preparations are made from them. The very name drug comes from the Anglo-Saxon word *drugon* meaning to dry. Crude drugs are the commercial form of plant drugs as they are brought to the market. They yield one or more definite chemical bodies of medicinal value which are known as active principles or active constituents. These constituents may occur in the whole plant or in one particular part, *e.g.*, roots, leaves, seeds, etc.

Besides the drugs of vegetable origin, there is another group of drugs known as chemicals. Many chemical compounds are produced by plants, by natural processes at ordinary temperature and pressure, *e.g.*, alkaloids, glucosides, salts, etc. To produce similar compounds artificially, the chemist has to resort to powerful reagents such as strong acids and alkalis, large variations

in temperature and pressure, distillation, fusion and many other drastic operations. Many of the products of the chemist are similar in action and composition to natural compounds, but they are cheaper to produce. Other chemicals belonging to the inorganic class are produced from natural minerals, sometimes by simple processes at other times by complicated ones. Then there are comparatively recent remedial agents obtained by various chemical operations, mainly from coal tar as well as other products obtained by the more or less complicated processes of synthesis. There are also the so-called organometallic compounds which form a powerful and important group, particularly in the treatment of protozoal diseases. These compounds have to be prepared with extreme care, as many of them would be positively dangerous, unless they are in a state of absolute purity.

The biological products, such as vaccines, sera, gland products, hormones, bacteriophages, etc., form another group of remedial agents. They require even greater skill and more expert knowledge than any other type of preparation used in medicine.

Action of drugs as basis of therapy. Pharmacology is the term applied to the science which deals with the action of drugs upon animal organism without special indication to their application in disease. It, in fact, denotes the physiological action of drugs, which forms the basis for their scientific use in curing diseased conditions, the alleviation and prevention of pain and prolongation of life. Experimental pharmacology deals with the reactions of living material to changes in environment, these changes being produced by drugs.

Therapeutics has been defined as the art and practice of treating abnormal states by any method that relieves pain, restores health or prolongs life. It comes from the Greek word *therapeutikas* meaning healing, curative, alleviative. It includes all remedial agents and measures used in the treatment of disease. Therapeutics may be empirical or rational. The former includes any measure which experience has shown to be beneficial but whose action cannot be explained, e.g., colchicum in gout; the latter consists in using drugs whose mode

of action is understood, *e.g.*, quinine in malaria. Some of the sub-division of therapeutics according to McGuigan are:—

(a) Mechanical, which includes the use of bandages, splints, dusting powders, petrolates, catheterization, massage, gymnastics.

(b) Drug or chemical therapeutics, which includes all substances acting chemically—therefore most drugs.

(c) Physical therapeutics or the use of heat, cold, electricity in various forms, or radium.

(d) Heliotherapy consists in using sunlight and other forms of light as therapeutic agents.

(e) Hydrotherapy or the use of water in all forms; ice, cold water, hot water, steam in the form of baths, packs, douches.

(f) Suggestive or psycho-therapeutics, includes suggestions, advice, hypnotism, or anything that will console or encourage the patient and so promote his welfare.

(g) Dietetic therapeutics or the regulation of the food, is always extremely important in the treatment and prevention of disease.

(h) Preventive medicine in a large degree may be considered a branch of therapeutics. It includes the use of all available hygienic measures in the prevention of disease or the limiting of its spread.

In the treatment of disease full use should be made of all these measures. In the improvement produced in the condition of the patient by application of these measures the part played by nature must not be forgotten. Nature is infinitely wiser in medicine and surgery than we imagine. Variations from normal in disease are often an effort on the part of nature to meet the needs of the patient and should not always be considered as harmful. Proper use of therapeutic measures renders important help to these forces in curing disease in the least time and with least harm to the organism. The task of the physician consists in directing the treatment in such a manner as to remove the obstacles which hinder the path of natural cure. This should be done by a thorough comprehension of the

diseased conditions, that is by diagnosing the case as carefully and as fully as possible. Before ordering a drug or method of treatment the physician should have a clear conception of what he is trying to accomplish. Drugs should not be prescribed unless there is a distinct indication for them. The doses of all the remedies should be very carefully considered, to fit the needs of the patient's condition. Special regard should be paid to such influential factors which have an important bearing on the treatment of disease as, the maintenance of the vitality of the patient by proper feeding, elimination of toxins by the kidneys, bowels and skin, relief of annoying symptoms, and giving to the patient sufficient physical and mental rest and sleep. Physicians should not be contented with the relief of symptoms alone but should strike at the root cause of disease. Unfortunately for a large majority of the diseases attacking man specific remedies do not exist. The progress of chemotherapy during recent years has produced a number of effective remedies against protozoal diseases, but drugs specifically attacking bacterial infections in the human body have not yet been discovered.

The mode of action of drugs. The drugs may act independently outside the body (antiseptics on micro-organisms), they may act in or about the body, but not on its structures (sulphur on ringworm of skins) and lastly they may act on the tissues of the body itself. On the tissues of the body the drugs may act by physical or chemical means.

(a) **Physical actions.** In these no chemical reaction occurs between the drug and the tissues. The examples of physical action are the protective effect of oils, dusting powders, etc.; osmotic effects or salt actions of isotonic, hypotonic or hypertonic solutions; adsorptive or absorptive action of carbon dyes, infusorial earths and the colloids generally.

(b) **Chemical actions.** Some drugs exert chemical reactions within the body which may be of the nature of combination or substitution. By combination is meant the direct union of the drug with the tissues of the body or with the products of secretion. Acids may unite with ammonia or with alkaloids to form addition compounds. Similar combinations may occur

with protein. The action of general anæsthetics is due to direct combination. Substitution occurs when the hydrochloric acid of the stomach is neutralised by sodium bicarbonate or the combination of calcium solution with oxalates to form inert insoluble compounds. Such unexplained reactions as selective affinity are probably chemical and may be either combination or substitution.

According to Straub the action of a drug is often due to the differences of concentration within and without the cell. Some drugs only act while they are penetrating the cell or while the concentration inside and outside the cell is different.

Selective or specific action. Selectivity is a phenomenon widely distributed in nature. The eye selects certain vibrations which are called light; other vibrations beyond the ordinary colour limit are unnoticed. The colour of objects is due to selective absorption. Foods and drugs are readily absorbed from the gastro-intestinal tract, cathartics are not. Carbon absorbs some gases and colouring matter to the exclusion of others. Platinum and palladium absorb some gases and not others. Selective oxidation occurs in the body, thus if 2.0 gm. of benzene are given to a man 0.8 gm. of phenol is formed, but if it is combined with 2.0 gm. of alcohol, all the alcohol is oxidised and only 0.33 gm. of phenol is formed. Selective actions in the body are apt to be modified by disease; sugar is readily oxidised in health but not in diabetes. The action of colloids may be selective. Other cases of selection may be explained on a physical or electrical basis.

The body cells show selective phenomena. The renal cells are very permeable to sulphates, the intestinal cells very slightly so. By virtue of this peculiarity the cells are capable of preserving their own composition notwithstanding the composition of the fluid in which they are bathed. This explains why a substance acts more strongly upon one cell than upon another. The differences are seen in case of the dyes. The difference in absorption may be due to the cell envelope and partly to the cell contents. Lipoid solvents generally penetrate better than other agents. The distribution of a drug is often modified by its reaction, or by the presence of a second

substance, such as oxygen. Iodides and acridine dyes are taken readily by degenerating tissues, such as, caseous material.

Most of the drugs exert their action by their chemical affinity for one or other constituent of protoplasm. The living cell may be considered as a complex laboratory, where chemical decomposition, synthesis, reduction and oxidation are constantly going on. Drugs act by altering these processes so that either the functional power of the cell or actual cell structure is changed. Some of these are general in their action, minute quantities affecting practically all forms of protoplasm in the body (though not all forms in the same degree) and when the action of drugs is powerful they are known as general protoplasmic poisons, *e.g.*, hydrocyanic acid, quinine, etc. To test the general protoplasmic poisons the effect is studied on bacteria, yeasts, white blood corpuscles, amoebæ, ciliary movements, spermatozoa, etc., *i.e.*, protoplasm undifferentiated into tissues or organisms. If the drug acts on these organisms, it is a general protoplasmic poison or has a general action. Some exert a selective action on a certain special tissue or tissues leaving the others unaffected. This is presumably owing to a chemical affinity for some component of the particular cells or group of cells. These are said to have a selective specific action. Strychnine has selective affinity for certain portions of the central nervous system, pilocarpine for secretory nerve endings, epinephrine for the sympathetic endings, atropine for parasympathetic nerve ending, picrotoxin for the medulla, etc.

It is suggested that during the production of specific effect the active drug is in some sort of combination with a chemical substance contained in the body of the cell acted upon and it is generally assumed that this combination is of a chemical nature. Adrenalin in producing its effect, is taken up and destroyed by the sympathetic nerve endings; strychnine forms a loose combination with the cells of the cord for it is all recovered from the urine unchanged, morphine comes midway between adrenaline and strychnine as it is partly destroyed in the tissues and if the animal is tolerant, destruction is much greater than normal.

Toxic effects. If drugs are given in adequate doses they produce therapeutic effects, but if larger doses are given they act as poisons. Poison comes from the Latin word *potio* meaning a draught. By poison is meant any substance, administration of which will injure health or cause disease. These effects may be immediately manifested or they may take some time to occur. Toxicology comes from the Greek word *toxikon* meaning a poison. It deals with the symptoms, diagnosis, treatment and detection of poison. As a large number of the drugs used in the treatment of disease are potent substances, their dosage and the length of period during which they are to be administered should be very carefully considered.

The nature and results of drug action. The fundamental properties of living matter as compared with dead matter are:—
(1) Metabolism, *i.e.*, functioning of anabolic and katabolic processes. This includes nutrition or assimilation, which includes digestion, secretion, absorption and excretion. (2) Excitability as manifested by contractility, conduction, irritability and secretion. (3) Reproduction.

Drugs can only modify these properties, they cannot create new functions. The changes produced by the drug are quantitative only. The smallest live unit is a cell and the body tissues are made up of infinite number of these cells. The effect of drugs on cells is to stimulate them, to depress them or to change or destroy them. Stimulation is an effect on cells by which their power or their readiness to function is increased. It is often impossible to separate stimulation and sensitisation. Normally all movements are increased by stimuli acting on nerve centres. Depression is a decrease in function due in most cases to decreased sensitivity. In irritation the change is more anatomical than functional, and some of the signs of inflammation (redness, rise of temperature, swelling and pain) are present. Drugs may cause fatigue and paralysis which are also modifications of function. The causes of fatigue may be:—(1) exhaustion of energy-yielding material, (2) accumulation of waste products. Fatigue occurs in the following order in tissues:—nerve centres, nerve endings, muscles and nerve fibres.

Recovery from fatigue takes place with rest alone. Paralysis may be produced by drugs and is due to a combination (chemical) of the drug with the cell substance; recovery takes place only after the drug is removed. Paralysis may also be caused by anatomical changes or lesions and in some cases recovery cannot be expected. In many cases fatigue and paralysis cannot be distinguished and in such cases both the elements usually enter into the action. Often a drug is found to stimulate one structure and depress another, *e.g.*, atropine stimulates the vagus centre and depresses the vagus endings; pilocarpine stimulates the nerve endings in sweat glands and depresses heart muscle.

The intensity of the action of a drug depends on, (a) the concentration in which it reaches the particular cells on which it acts and, (b) the duration for which this concentration is maintained. The concentration which a drug attains in the body depends on:—(1) The rate of its absorption, and (2) the rate of its removal from the body which occurs in two ways:—(a) Excretion by kidneys, lungs, skin, etc. (b) Chemical destruction in the body by compounds, processes of oxidation or reduction, or by the formation of inert bodies in combination with such compounds as glycuronic acid and sulphates.

Absorption and distribution of drugs. The local action of drugs occurs without absorption and general action only occurs after absorption. There may however be local, general and specific actions from the same substance, *e.g.*, phenol. In many cases the object of administration is that they may be absorbed into the blood and produce their specific effects. For this purpose a drug may be (1) applied to the skin, but here absorption takes place with difficulty, as it has to be completed through the sweat glands, the horny epithelium of the skin being impermeable; (2) when administered by the mouth the drugs are absorbed from the gastro-intestinal tract; (3) when injected subcutaneously, intramuscularly, intravenously or into one of the serous sacs absorption rapidly takes place.

When given by the mouth, which is the commonest mode of administration, drugs are absorbed principally by the upper portion of the small intestine; very little absorption occurs from the stomach though alcohol and strychnine are absorbed

slowly from it. Experiments have shown that the isolated rectum absorbs at least as well as the small intestines, owing to its abundant vascularity. Strychnine $1\frac{1}{2}$ grain put directly into the stomach of an animal produces convulsions in 30 minutes, in the small intestines in 10 minutes, in the œsophagus in 50 minutes, in the colon in 14 minutes and in the rectum in 7 minutes. From the stomach most drugs are absorbed slowly under ordinary conditions. Alcohol is, however, an exception and is not only absorbed rapidly but accelerates absorption of other substances dissolved in it, because its irritating effect improves the circulation. Such effects are reversible and the absorption of alcohol may be slowed by non-absorbable drugs like cascara sagrada. Substances like oleo-resin of male fern are absorbed more quickly from solution in oil than in water. Absorption from both the stomach and intestine is influenced considerably by the amount of food present and in some cases the food enters into combination with the drug. Absorption is more rapid from the empty than from the full gastro-intestinal tract. Absorption occurs readily from the small and more slowly from the large intestines. Foodstuffs that are not absorbed from the small intestines, are often absorbed from the large gut. In medical practice rectal feeding has sometimes to be resorted to in persons unable to swallow; predigested foods and glucose are readily taken up. Toxins are also absorbed in the same way. The rate of absorption depends on the method of administration of a drug and occurs in the following order beginning with the most rapid, intravenous, intraperitoneal, hypodermic routes, through mucous membranes of sublingual region, nose, stomach, rectum and from skin. Conditions affecting the alimentary canal also modify absorption, thus in shock absorption is considerably decreased. Slight irritation of the gut which does not cause injury may facilitate absorption. Pronounced injury may decrease it; ulceration of the mucous membrane increases the absorbability of many drugs. Astringents tend to lessen absorption, and saline solutions such as magnesium sulphate and other cathartic drugs, which are but little absorbed themselves, may prevent the absorption of other drugs and even water.

The mechanism by which the mucous membrane of the gut allows the ready absorption of some substances and inhibits that of the others is not understood. Why K or Cl ions are absorbed and SO_4 and Mg ions are not, is not clear. The intestinal epithelium undoubtedly must have some selective power. It should also be noted that the presence in the alimentary canal of non-absorbable substances hinders absorption of others, *e.g.*, absorption of strychnine in the isolated piece of gut is delayed in presence of magnesium sulphate. Some gases such as hydrocyanic acid, phosgene, nitrous oxide, and ethylene are absorbed rapidly by the lungs, while ammonia is but little absorbed.

Only soluble substances can be absorbed, but it should be remembered that solubility is modified by chemical changes in the alimentary canal; insoluble substances are rendered soluble by the action of juices and are then taken up. Solid substances such as carbon, iron, etc., are taken up through the agency of phagocytes and may be found in the mesenteric blood and lymph nodes. Such solids exert no action unless dissolved in the body fluids. The rate of absorption is modified by the solvent. Solutions in alcohol are more rapidly absorbed than water solutions. The more soluble a substance is in protoplasm, the more quickly it is absorbed. The concentration of the solution may vary the rate of absorption. The absorption area modifies the rate of absorption, *e.g.*, multiple hypodermic injections are absorbed much more quickly than if the same amount of fluid were injected in one place at once.

Volatility is another factor which influences absorption. Hydrocyanic acid is absorbed rapidly and causes instantaneous death when concentrated. Most volatile substances if swallowed are rapidly absorbed from the gastro-intestinal tract. Colloids such as gums and resins, oils, kaolin (Fuller's earth) charcoal and other inert powders and plant residues, when mixed with absorbable materials such as salts and alkaloids, lessen the rate of absorption—partly by fixing themselves to the drug and partly by hindering access to the absorbing surface. Isolated active substances (alkaloids) are, therefore, preferred if quick systemic action is desired, while galenical preparations (extracts, tinctures, pills, etc.), are used for local

effects. No general action may take place if the excretion of a drug is as rapid as its absorption, because the effective concentration cannot be maintained.

Rapidity of absorption is proportional to the rapidity of the circulation and flow of lymph through the part. In cases of heart disease where there is stasis in the circulation of the intestine, digitalis may be poorly absorbed, and this accounts for the failure of digitalis therapy in these conditions. For the same reason lesions of the spinal cord delay absorption. Vasoconstriction and catarrhal conditions of the intestines may also reduce absorption. Excessive distension of the gut decreases the rate of absorption by slowing the blood and lymph flow. Although drugs like arsenic may travel for a considerable distance through dead bodies and strychnine, morphine, fuchsin, epinephrine, etc., have been shown to be absorbed in frogs with the heart removed, absorption normally takes place only when the circulation is intact. In the alimentary canal, injury to absorbing cells may either facilitate or hinder absorption.

Absorption by the blood and lymph. Most soluble substances are absorbed from the alimentary canal by the blood rather than by the lymph and this is also true of serous cavities. Such substances as methylene blue, methanamine and some other drugs injected into the pleural sacs appear in urine before they are seen in the thoracic duct. All these drugs, however, may be detected in the lymph. Some potent toxins such as tetanus and diphtheria when injected locally, follow the nerve sheath to the central nervous system. Such toxins are more active when given intramuscularly or subcutaneously than when given intravenously, because by the last route they reach the centres in a more diluted form.

A large number of drugs are either not absorbed at all or only in minute amounts. Of the common metals only arsenic and mercury are readily taken up and both of these are volatile; most of the heavy metals are absorbed so slowly that weeks or months of ingestion may be required to produce poisonous effects. Injection into the circulation of the same amount of iron, as given by mouth, may be attended with serious results.

The difference in toxicity here is largely a question of absorption.

Absorption through the skin in man is very slow, though some substances such as methyl salicylate may be rapidly absorbed. The skin of young children is more permeable and death has occurred by application of methyl salicylate in this way. Absorption occurs more rapidly from regions where the epidermis is thin, *e.g.*, axillae, groins, inner surface of arms and thighs. That is the reason why inunctions are given in these regions. Potent drugs such as atropine and aconite, should be applied with care. If absorption is required from the skin, the drug should be incorporated with lanoline or lard. Lanoline is said to carry the drug to the tissues, lard to the skin only and petroleum to the surface of the skin. Absorption occurs quickly from the pleural and peritoneal cavities. Hyper-tonic salt solutions first draw water from the blood and when they are isotonic they are rapidly absorbed.

Absorption is delayed by emotional states; fear, pain and sorrow may seriously interfere with the emptying of the stomach, digestion and absorption. Many pathologic conditions delay absorption. Absorption of fat is delayed in tuberculosis of the intestines on account of destruction of the lymphatics. In extra-intestinal tuberculosis the absorption of all types of food materials is reduced by one-half. Deficient circulation delays absorption, some absorption occurring through osmosis and diffusion even in the absence of circulation.

Some drugs produce their effect because they are not absorbed. A good example of this is the purgative group of drugs. Unabsorbability is the essential of a good purgative. It is for this reason that pure crystalline active principles are not good as purgatives, since in this form absorption is facilitated.

Sojourn of drugs in the blood. A drug, once it is absorbed into circulation, stays in the blood for a short time, because it must penetrate into the tissue cells to produce its effect. The passage of the absorbed or injected substances from the blood into the tissues is a rapid process for diffusible substances and materially slower for colloids. Intracellular absorption is a very

rapid process and depends on the nature of the drug and to some degree on its concentration. Toxic doses of arsenic, after intravenous injection, disappear completely from the blood in less than 30 seconds, diphtheria toxins take 4 minutes, cyanides 2—6 minutes; anti-toxin circulates for several hours. A group of dyes remain for longer periods in the plasma, another group are rapidly excreted by the urine; and a third group disappear from the plasma, but are not excreted by the kidneys.

Distribution of drugs in the body. This is not a uniform process. Drugs accumulate particularly in certain cells, according to their permeability and physical and chemical affinities. These influence their action either by bringing them in contact with reactive tissues, or storing them in places where they may be inactive. Iodine is stored in the thyroid gland as iodothyron; bones retain earthy metals and fluorides; heavy metals are deposited as loose organic compounds in the liver and the spleen; mercury as a loose globulin compound; arsenic as a more stable nuclein combination occurs in the liver, bone marrow, skin, etc., chlorides, bromides and related ions accumulate in all organs but mainly the skin and the blood. Little is known about the distribution of organic poisons, mainly for want of suitable assay methods.

Changes in drugs during absorption. The majority of drugs are altered in the body by processes of oxidation, reduction, hydration, dehydration or decomposition; by storage in certain organs, or combination with other substances, toxic drugs are rendered harmless. This process of detoxication is of very great importance as it renders the continuous administration of drugs (in most cases in increasing doses) an absolute necessity. If it were not for this power of the organism to destroy and remove poisons and thereby to recover from its action, all therapeutic uses of drugs would have been an impossibility. On the other hand, the alteration of the drug by the body may result in the formation of more toxic substances (nitrites) or the drug may be rendered more effective therapeutically. The digestive juices destroy some organic poisons by hydrolytic changes (glucosides, proteins and anti-toxins). They are also necessary to saponify and liberate

the active constituents of insoluble esters (phenyl salicylates). The acidity of gastric juice is of importance in the solution of bases.

The tissues play a part in decomposing toxic drugs. Strychnine, morphine and many other alkaloids are partly oxidised in the tissues and thus rendered inert. Many organic acids, alcohols and formaldehyde are detoxicated by oxidation. The organic compounds of metals (*e.g.*, cacodyles) only develop their metal action after oxidation. The thyroid gland is said to play an important part in destruction of poisons in the body and its excision increases the toxicity of many poisons. The liver is believed to be a great disintoxicating organ, acting partly by destroying poisons and particularly by storing them. That is the reason why the same dose is much less effective when given into one of the mesenteric veins than when given by the jugular vein. This has been shown to be the case with curare, strychnine, morphine, cocaine, narcotine, quinine, atropine and the metals. Perfusion of alkaloids, glucosides, toxins, barium, etc., through the excised liver decreases their toxicity. Perfusion through excised muscle also produces disintoxication, but its action is weaker than that of the liver, in case of chloral, atropine, physostigmine, alcohol, etc. Excision of the spleen is said to increase the toxicity of most alkaloids, but not all. The phagocytes accumulate and thus disintoxicate many poisons, especially the colloids. The serum of atropine-resistant animals (rabbit) destroys atropine.

Adsorption. Adsorption comes from the Latin word '*Sorbere*' meaning to suck. It is the power possessed by certain substances of retaining on their surfaces gases, liquids, and solids, either in solution or in the colloidal state. One substance here becomes a part of another and remains in a state midway between mechanical mixture and chemical combination. This phenomenon plays a very important part in the action of drugs. The disintoxication is sometimes carried out through adsorption, thus pilocarpine is detoxicated for excised intestine by digestion with serum; but it may be fully recovered from it in active form by extraction with acid or alcohol, showing that it was not destroyed. The nature of adsorbing substances is not

known, but it is found in abundance in rabbit's serum, less in that of cats or oxen, and it is absent in dog's blood.

Disintoxication by combination. Phenols and other aromatic compounds are rendered less toxic by combining with sulphates; many metals are detoxicated by proteins; toxins by anti-toxins; acids by alkalies; benzoic acid by glycocoll, etc. The extent of the disintoxication depends on the activity of the metabolic processes which are concerned, or on the amount of neutralizing substance present in the body.

Excretion of drugs. The main channels of excretion are the kidneys and bowels, and with volatile drugs the lungs. The sweat and for that matter other secretions play a comparatively minor part. The relative importance of different channels varies for each drug. The excretion is proportionate to the circulation of the blood and may be increased by factors which stimulate it. The excretion of certain drugs is limited by their being in the body in the form of combinations; the elimination of these is favoured by substances which displace them in the compounds (excretion of iodides is increased by giving chlorides).

Certain drugs are excreted by sweat, *e.g.*, iodides, bromides, borates, phenol, salicylates, antipyrin, methylene blue, arsenic and mercury. The quantities thus got rid of are too small to be of any significance from the point of view of elimination, but they help to explain certain skin conditions which accompany their administration. Excretion by saliva is limited to iodides, potassium, ammonium, mercury, lead, menthol, guaicol and some alkaloids (morphine and quinine). The excretion generally begins within 20 minutes and lasts for nine hours.

Passage into cerebro-spinal fluid. Organic substances get into the cerebro-spinal fluid to a very small extent; iodides and bromides are present in traces. Many organic substances pass in more freely, thus alcohol, chloroform, acetone and methanamine occur constantly in about one-third the concentration of the serum; aniline dyes are not generally found in the cerebro-spinal fluid, or in the gray matter of the brain after intravenous injection; those which are liposoluble are found in the gray matter. The passage into the cerebro-spinal fluid varies

with the species of animal; thus picric acid penetrates in dogs, cats and guinea pigs, but not in rabbits.

Passage to foetus. Chloroform, ether, alcohol, chloral, ethyl bromide, scopolamine, quinine, atropine, morphine, arsenic, mercury, potassium iodide, potassium bromide, carbon monoxide, salicylic and benzoic acid, phloridzin, nitrates, urea, methylene blue, pass into the foetus if given to mother. The placenta acts as an ultra-filter towards colloids. The colloidal dyes and proteins do not pass into the foetal circulation.

CHAPTER II

CONDITIONS MODIFYING THE ACTION OF DRUGS

The action of drugs in the body is dependent on several factors:—

1. The first thing to be considered is the dosage. By this is meant the quantity of a drug required to produce action either immediately or after repetition. The largest quantity which can be given without untoward effects is called the *Maximum dose*. Young persons require smaller doses than older ones, since younger tissues react more readily and also because the weight is less. In children the dose is usually given according to age.

Many practical rules have been devised for calculating the doses for children when the adult dose is known.

(a) Young's rule:
$$\text{adult dose} \times \frac{\text{age}}{\text{age} + 12}$$

(b) Cowling's rule:
$$\frac{\text{adult dose} \times \text{age at next birth day}}{24}$$

If prescribing 24 doses all that is required is to multiply the adult dose with age of the child in years.

(c) Bush's rule. Multiply the age by 5, this gives the percentage of the adult dose.

In this connection Clark has formulated a method of dosage for a person of known weight—
$$\frac{\text{adult dose} \times \text{weight of person in pounds}}{150}$$
 150 lb. is taken as average weight of an adult person. This method, though useful, is not always feasible as it is impossible to weigh a patient lying in bed. A rough estimate of the probable weight can, however, be made.

A single dose may be given or divided doses may be administered ($\frac{1}{4}$ gr. calomel every half hour till 2 or 4 grains are taken). Repeated doses may be given (1) to have effect just at the time of administration, or (2) to have continuous effect (digitalis for disordered heart).

Cumulative action. The repetition of a drug produces greater effects than the first dose. Toxic effects may be produced by repeated administration of drugs. This may be due to (1) the amount of drug excreted being less than the amount absorbed. Such drugs are called cumulative poisons, *e.g.*, digitalis, arsenic, mercury, lead, etc.; (2) it may also occur when the excretion is decreased or suddenly stopped for some reason (nephritis), or (3) a sudden solution and absorption of a sparingly soluble drug owing to some change in intestinal content. Successive doses of the drug may remain unabsorbed in the alimentary canal, in the muscle or subcutaneous tissue, to be finally taken into the system when the conditions are more favourable for absorption. It sometimes happens that effects are more easily reproduced after they have been once induced. This is particularly the case with drugs acting on the central nervous system. Susceptibility to strychnine increases with its administration and is said to be due to the central nervous system becoming educated to the stimulating actions and responding to them more.

Pushing a drug to its *physiological limit* means to give the remedy in increasing doses till toxic symptoms appear.

1. **Dosage and effect.** A drug may have different effects according to the dose in which it is given, *e.g.*, ammonium carbonate is an expectorant in 3—10 gr. doses and an emetic when 30 gr. are given. It should be remembered that body weight has an important bearing on dosage and in prescribing drugs this should always be taken into consideration. In pharmacological experimentation, it is customary to estimate dosage in proportion to weight and within certain limits, this should be a good method for human beings. Smaller persons require less than larger persons. The required dose of most drugs is nearly proportionate to the body weight.

2. **Habit** usually lessens the effect of drugs to some extent; persons habitually using morphine or opium need bigger doses of these drugs; persons taking large doses of alcohol need larger doses of hypnotic and anaesthetic drugs. In a few cases the reaction is greater after continued use, as in case of the purgative *cascara sagrada*. In the case of habit-producing

drugs tolerance may be largely psychic. The nervous centres learn to modify the reactions so as to adapt them to drug environments. When this environment is abruptly altered by withdrawal of the drug, there is generally extreme discomfort, resulting in craving and great nervousness, constituting abstinence symptoms. Functional habituation, when acquired for a particular drug, may hold also for other drugs having a similar action.

3. **Sex.** Women are more delicate and lighter than men and need four-fifths of the dose of men. Idiosyncrasy occurs more often in the female sex; during the menstrual period certain drugs are not advisable (*e.g.*, quinine causes hæmorrhage). Pregnancy and lactation should also be taken into consideration as some drugs are excreted in milk, while others have action on the gravid uterus.

4. **Time of administration.** This is of importance, *e.g.*, saline cathartics act most rapidly on an empty stomach after a period of fasting, so they are usually given in the morning before breakfast. The more slowly-acting purgatives are given at bed time and half an hour before meals. Irritant drugs, such as arsenic or iron, are best given after meals, when they become well diluted with the stomach contents and come in contact with the stomach wall in lesser concentration and do not irritate it; quinine sulphate is best given $1\frac{1}{2}$ to 2 hours after meals, because it is more quickly absorbed when the contents of the stomach are acid and besides it is less liable to disturb digestion at this time; digitalis preparations are best given by themselves on an empty stomach. Soporific drugs are most effective at the natural time of sleep; they may be without effect if the patient is not in bed and is up and about. Sodium bicarbonate is given on an empty stomach because, if given during the digestive period, it neutralizes the hydrochloric acid of the gastric juice.

Relationship between the time of administration of a drug and meal-time may influence not only the rate of absorption, but also may modify its action. Given on a full stomach, the absorption is slower than when given some hours after meals;

if local action is desired on the stomach, the drug should be given before meals.

5. Climate in which a person lives renders him more or less susceptible to certain remedies, *e.g.*, alcohol is better borne in cold climates. The temperament of an individual is an important factor; phlegmatic dark-skinned people react to drugs less readily than blondes and nervous patients, especially in respect of drugs which act on the nervous system.

6. The preparation employed is also a matter of importance; whenever possible, a standard preparation should be used (pure alkaloid).

7. **Idiosyncrasy and susceptibility.** Drugs may exert an unexpected effect either by having an unusual action or failing to produce ordinary action. The term idiosyncrasy is applied to peculiar, exceptional reactions to the effect of drugs. It is a condition of increased susceptibility to a remedy. There may be quantitative hyper-susceptibility to ordinary actions of drugs, so that side actions, which are ordinarily negligible, become greatly accentuated. Neurotic individuals are subject to psychic exaggeration or modification of drug effects through fright, excitement or suggestion. They are frequent causes of disappointment both to the physician and the patient and may give rise to excessive action from what has been thought to be a moderate dose.

Allergic hyper-susceptibility is a type of idiosyncrasy in which the patient reacts to special substances, food or drugs, by irritant oedema and spasm of smooth muscles, urticaria, bronchial asthma and collapse. It is generally hereditary but not congenital, *i.e.*, it may manifest itself in later life. It resides in the tissues so that it cannot be transferred to the blood serum. It can be induced in excised tissues by treatment with colloidal precipitants. Some people develop a rash or even very serious symptoms after eating strawberries, others after taking certain kinds of fish. Sometimes all members of a family show such an idiosyncrasy to a special article of food or to a particular drug. Thus it has been reported that a minute amount of cocaine dropped into the eye or a few grains of quinine taken internally have produced very serious symptoms. The cause of this

condition is not quite clear. Slight alteration in the composition of tissues may cause similar conditions, *e.g.*, deficiency of calcium renders the whole autonomic nervous system more susceptible to the action of certain drugs. The variations in reactions of different animals or racial idiosyncrasy can be explained by difference in physiologic functions; for instance, cerebral reactions are usually predominant when the central nervous system is highly developed, while spinal reactions predominate in lower vertebrates. Rabbits are incapable of vomiting, therefore, they cannot be affected by emetics. Atropine quickens the heart in dogs but not in rabbits, because it paralyses the vagus which is not tonically active in this animal. The dog-fish is more or less resistant to nephrotoxic poison as it normally excretes urea and other metabolic products through the gastro-intestinal tract. Normal resistance may be due to destruction of the poison, *e.g.*, atropine by serum of rabbits. Differences of absorption and excretion also come into play. There are many factors, however, which cannot be satisfactorily explained. The resistance of the hedgehog to poisons like morphine, nicotine, atropine, cyanide and arsenites and not to strychnine, cannot however be explained. It should not be forgotten that abnormal reactions following the administration of drugs may rarely be due to the presence of impurities.

8. **Tolerance.** Some animals and men fail to react to drugs even when given in considerable doses and this phenomenon is known as tolerance which may be natural or acquired, *i.e.*, developed by repeated administration of a drug. Natural tolerance may be due to the power of the tissues to neutralise poisons. Thus carnivora can stand large amounts of acids owing to the production of ammonia in their tissues; chickens are immune to oxalic acid when given by mouth, because of the large amount of calcium in their intestines.

Acquired tolerance is the result of habituation to drugs. This may be functional (alcohol, caffeine, nicotine); or it may be due to diminished absorption (arsenic), to increased elimination (atropine in cats), to increased destruction of poison (morphine) or to production of antibodies (toxins). The tolerance

is usually limited, not absolute. Any condition which lowers the general resistance of the animal increases its susceptibility to the poison (frog in tepid water). Tolerance differs from immunity in that anti-toxins are said to be formed in the latter. Anti-toxin formation, however, is an instance of acquired tolerance. It was supposed to be confined to proteins, but it appears to exist also towards certain glucosides (toad-stool and snake venom). It does not occur with alkaloids. It has not been shown that any chemical substances except proteins produce anti-bodies.

9. Effect of disease and pathological conditions. Many pathological conditions modify drug action. The effect of drugs in disease may differ materially from that in health. Antipyretics reduce temperature in fever but not in health; bromides lessen nervous irritability more in epilepsy than in health; morphine in pain lessens sensitivity but has less effect in health; in malaria quinine is tolerated in much larger doses than in health; antimony compounds are tolerated better in kala-azar. Pathologic conditions may modify absorption and excretion. Suppression of urine, as in nephritis, may lead to toxic symptoms from drugs and in doses which are ordinarily harmless. Absorption of poisons is hastened immediately after hæmorrhage. Inflamed vessels react abnormally, epinephrine may produce dilatation and caffeine constriction of the vessels, in a rabbit's ear. Diseased intestines allow much more rapid diffusion of proteins, toxins and ferments than healthy intestines. The distribution of the drug in the body may differ in health and disease. Iodides and many dyes tend to accumulate in the necrotic areas of tuberculosis, tumours, etc. Diseased conditions may lessen absorption (*e.g.*, in diarrhoea) or increase it (*e.g.*, in corrosion or ulceration of gut); they may accelerate destruction of poison (alcohol produces less intoxication in pneumonia) or they may alter the effect entirely.

10. Synergism and antagonism. A drug exerts its usual activity much more easily if it is given with some other drug of the same class, and it is found that combination of two drugs having the same action will give a result which one alone will not produce, however large the dose might be. Such drugs are

called synergists or mutual helpers and the phenomenon is known as synergism. In some cases new actions develop by the reaction of drugs with each other, with the production of new compounds (acid renders the basic salts of bismuth soluble and toxic).

Synergism of drugs was responsible for combination therapy which had the idea of securing summation of the desirable effects of several drugs; the side actions usually do not increase and in some cases they are neutralised. Formerly this form of therapy was popular and shot-gun prescriptions were given with the idea that some at least of the many ingredients might attack the disease. Such indiscriminate empirical use of drugs, however, is not scientific and it is better to employ only a few drugs with known actions. More recently, the combination method has been tried with great success by Ehrlich in treatment of protozoal diseases, for this is the principle underlying chemotherapy. In combining several drugs having a similar action the dose of each should be correspondingly reduced.

The best examples of synergism are seen in the group of narcotics. In the case of alcohol, ether and chloroform the effect is simple summation, but in case of morphine and scopolamine there is considerable potentiation of effects. Again an injection of magnesium sulphate considerably helps the action of ether in the production of general anaesthesia. A mixture of purgatives, *e.g.*, calomel, jalap and colocynth, act better than a single purgative.

The potentiation may be produced by one drug modifying the penetration of the other into the cell, altering the chemical affinity or attacking the cell from a different point of view. Magnesium potentiates urethane, and ether potentiates chloral or morphine, by favouring their distribution in the central nervous system.

On the other hand, a drug may lose a part or all of its action because of some agent which has the opposite physiologic effect. Such opposing agents are called antagonists and the phenomenon is known as antagonism. There are examples of antagonistic substances being manufactured by the body itself (epinephrine and thyroxine). The antagonism between drugs and

poisons when this depends on the antagonistic innervation of certain organs is easy to understand (*i.e.*, vasodilators and vasoconstrictors). Much more difficult to understand is the antagonism by which one drug overcomes the effect of another in the same cell without the aid of physiological mechanism. This may be brought about in two ways:—

(1) By chemical changes or combination as in case of free acids and alkaline carbonates, oxalates and lime salts.

(2) By true antagonism, as in case of atropine and muscarine, which is of truly physiologic nature, for these two drugs have no chemical affinities for each other, but produce directly opposite effects on the same organic element. The action of potassium chloride and ammonium chloride on the yeast ferment invertin, gives a simple type of this antagonism, the first inhibiting and the latter favouring, and the two together in proper proportions leaving the activity unaltered. In other words, there is complete reciprocal antagonism. The possibility of this has been denied on the ground that while it is possible to bring about paralysis in a stimulated organism, it is not possible to bring about stimulation in a paralysed one. It must not be forgotten, however, that combination between poison and protoplasm is of a dissoluble nature, so that cells may be restored again and poison washed out from them if bathed with blood which is free from the poison. Reciprocal antagonism between calcium and magnesium and sodium and potassium is clearly demonstrated in living organism, for the tissues can maintain their normal function, particularly their normal excitability, only when these kations are present in their correct relative proportions.

Antagonistic drugs may act, (*a*) on the same structures, *e.g.*, bromide and strychnine on the spinal cord; caffeine and alcohol on psychic and motor centres in the cerebrum; pilocarpine and atropine on the vagus nerve-endings; (*b*) on different structures, *e.g.*, digitalis slows the heart by stimulating the vagus centre, atropine prevents this by depressing the vagus nerve endings. Adrenalin contracts vessels by stimulating the vasoconstrictor fibres while nitrites relax them by acting on the muscle fibres.

CHAPTER III

MODES OF ADMINISTRATION

By mode of administration is meant the way in which a remedy is to be used. Remedies are given to obtain either direct local action, a remote local action, a systemic or general action.

(1) **The direct local action** of a drug is exerted at the place at which a drug is applied, *e.g.*, skin, nose, urethra, etc. Locally, drugs may act by protection, irritation, or depression of sensory nerve endings or other tissues. Many drugs act locally only, others like strychnine, exert little or no effect at the point of application, but exert a marked general effect. Local remedies may or may not require to be absorbed, *e.g.*, bismuth subnitrate for an irritated stomach, talc powder for skin which is chafed.

(2) **Remote action.** Remote or indirect action is an action elicited on organs away from the site of application. Such action of drugs may appear (a) after its absorption into the circulation, *e.g.*, of strychnine on the spinal cord; pilocarpine on the secretion; (b) without actual absorption, *e.g.*, irritation of the skin, blisters or cold applications influence the rate of the heart, indirectly through the central nervous system. Sometimes the effect of a drug is manifested as it is being excreted, *e.g.*, irritation of the bowels and kidneys by perchloride of mercury as it is passed out *via* the colon and the urine; anti-septic action of urotropine as it is eliminated in the urine.

(3) **The general action** is one that cannot be fixed in any particular tissue, *i.e.*, the action of many tonics and sedatives.

The effect of a remedy depends largely on the way in which it is given, *i.e.*, adrenaline given by mouth has a local action on the stomach only, while if given hypodermically or intravenously it produces an enormous rise of blood pressure. A dose of saponin by the mouth is perfectly harmless, but it gives rise to poisonous symptoms if given under the skin. Some tissues and organs absorb much more rapidly than others,

therefore, larger quantities of the drugs, pass through them into the blood in a given time. For instance, if a poison which is absorbed slowly, be rapidly excreted, so little of it will exist in the blood and tissues at a time that hardly any action is produced; while if it is rapidly absorbed by some other method of administration, even a small dose will exert some action before it is excreted, *e.g.*, potassium salts given by the mouth are not poisonous in large quantities, but when given hypodermically or intravenously they produce toxic effects to certain organs.

The channel by which a drug is introduced into the body or the place to which it is applied, must necessarily vary with the object to be secured, *i.e.*, whether the action is to be purely local or general; whether rapidity of absorption is desired or whether there is any necessity of avoiding irritation to certain organs, etc.

1. **Local application.** Locally, drugs may be used to protect surfaces, for producing reflex effects, for antiseptic or stimulant purposes.

On the skin, drugs may be applied in various vehicles. If it is desired the drug should penetrate deeply or be absorbed it should be mixed with animal or vegetable fats. The reason is that although the lower layers of skin absorb readily, the stratum corneum of the epidermis is non-permeable to most substances. The absorption takes place through the glandular structures which are filled with fatty matter. Increased vascularity of the skin favours absorption by carrying away quickly the absorbed drug. Where local effect alone is desired, mineral fats (vaseline) may be used. Oils and ointments delay the absorption of fat-soluble substances, such as phenol, mustard oil, etc.

Local application to the skin has to be used for producing general effects in those cases where the stomach must be avoided and the subcutaneous method is not practicable, *e.g.*,unction of mercury. The objection to this method is that (1) absorption is uncertain and consequently exact dosage is impossible, (2) the absorption is greatest where the skin is

most delicate (axilla, loins, inner surface of the extremities). Absorption is aided by rubbing.

Watery solutions as a rule are not absorbed from the skin but when the solutions are brought in intimate contact, certain salts may be absorbed. Skin is capable of absorbing sulphuretted hydrogen and other gases. Application of watery solutions to the abraded skin or open wounds is, however, quite a different matter. Absorption under such conditions, takes place readily and the rate of absorption is practically similar to that obtained by subcutaneous injections. Chronic and callous ulcerations with defective circulation are, however, poor absorbing surfaces.

Cataphoresis or ionic medication. Many drugs, which are not ordinarily absorbed through the skin, may be made to do so by means of an electric current. This method is known as ionisation. Convulsions have been produced by driving strychnine into the tissues by ionisation. For further details of the method, see the chapter on physiotherapy.

On mucous membranes: Drugs can be applied locally to surfaces other than skin, *e.g.*, mucous membranes. The conjunctiva absorbs readily, so that apart from local action, a systemic effect of drugs may, sometimes, be produced, *e.g.*, atropine. A few milligrams of apomorphine in the conjunctival sac of a dog produce vomiting. The vagina absorbs freely and clinical poisoning may be produced by giving the drug in the form of douches. The uterine cavity also provides a very good absorbent surface. The urethra absorbs readily and frequent poisoning has occurred from application of local anæsthetics. The urinary bladder absorbs poorly; drugs like strychnine, apomorphine, morphine, etc., are quite harmless when given by this way. The ureter and renal pelvis absorb fairly well.

Sprays are finely atomised solutions and are inhaled for their local action on the mucous membrane of the nose, pharynx and larynx. They must not be too irritant. To reach the lower air passages they should be deeply inhaled with the nostrils closed, the mouth widely opened and the tongue slightly protruded.

Insufflation. Powders are frequently blown on to a surface, *e.g.*, boric acid into the ear or relatively inaccessible parts.

Inhalations. This method is used for gaseous medicines such as anæsthetics, oxygen, etc. The effect depends on the concentration of the gas and the time during which it is administered. The action is most rapid as they reach the blood stream quickly. The capillary surface of the lungs, which is only separated from the alveolar air by a single layer of flattened epithelial cells, is wonderfully adapted for absorption of volatile substances into the blood. The chief advantage of this route of administration is the possibility of controlling the amount of drug at any desired time. The effect also disappears quickly after the drug is discontinued.

The lungs also absorb fluids and dissolve substances rapidly if these are introduced through the trachea. A continuous stream of warm water given into the trachea of a horse, at the rate of 6 litres per hour was absorbed ; no trace of water being found, though the animal died of direct injury to the lung tissue. Rabbits can receive 30 to 40 c.cm. of fluid into the trachea. If the fluid is injected more rapidly than it is absorbed it fills up the alveoli and produces asphyxia. This route of administration is, however, not used in therapeutics on account of the danger of asphyxia.

Inhalations for local action. These can be effectively employed by evaporating the substance with steam, either by placing it on boiling water and inhaling it through a funnel, or by the steam atomizer. The steam gets condensed on the surface of the mucous membrane and the drug is deposited at that area. Even with deep inhalations the vapour does not go beyond the larger bronchi. The respiratory movements, however, tend to distribute the material widely through the lungs. In many affections of the nasal and upper respiratory passages this method is very commonly used.

Intratracheal injections. Small quantities 2 or 3 c.cm. of oily solutions (*e.g.*, menthol) may be injected directly into trachea through the glottis. They then are distributed by respiration similarly to those by sprays and steams. The advantage is not apparent.

2. Oral and rectal administration. Oral administration is the most ancient method and is still the method of choice with most drugs. Drugs whose general action is desired after absorption are generally given by this way, but sometimes drugs may be given for their local effect by this route also (*e.g.*, bismuth and emetics for their action on the stomach, vegetable purgatives on the intestines).

Some drugs give rise to disturbances of digestion when given by the mouth. This can be avoided by giving them

in the form of pills coated with keratin, in capsules or cachets so that they will not get dissolved in the stomach, or they may be given when the stomach is full so that they are diluted. Absorption mainly takes place from the small intestines.

Rectal administration may be used to avoid the action of a drug on the stomach and the small intestine. The rectum, on account of its profuse vascularity and venous plexuses, is a very good absorbing surface for many soluble substances so that effects are often more prompt and more marked than with the oral method. Absorbed substances also do not pass through the liver where they are liable to be destroyed. The drug is given in the form of an enema or suppository. Enemata when given for absorption should be as small as possible (2 ounces) and not irritant. The rectum should be washed out with warm water before they are given. About twice the dose given by the mouth is necessary to produce the usual effects.

The rectal administration of drugs has been practised since the time of Galen and although its utility is limited, it still occupies a very large place in therapeutics. As many drugs are fairly well absorbed from the rectal mucous membrane, there is a growing idea that this route of administration may be resorted to in supplying nutriment to the system whenever occasion demands it.

Rectal feeding. The use of nutrient enemata or suppositories containing food materials is based on the assumption that absorption takes place from the rectum and the large bowel. The absorption of foodstuffs from the rectum is, however, very limited. Physiologically, the rectal mucous membrane is unsuited for the purpose of digestion and absorption of nutrient material. The main digestion of food, as is well known, takes place in the small intestines. The pancreatic juice furnishes powerful ferments which digest starch (amylase), fats (lipase) and proteins (trypsin). The bile renders important assistance in the digestion of fats. The secretion of the mucous membrane of the intestines (succus entericus) also possesses an important digestive function through its ferment 'erepsin.' After the digestion is completed, absorption takes place through the highly specialised epithelium of the villi of the intestinal mucosa. Practically the whole process of digestion and absorption is completed in the small intestines before the material is transferred through the ilioæcal valve into the large

intestines. In the large intestines absorption of water chiefly takes place. 'Erepsin' is the only ferment present which can break down proteoses and peptones only into the simpler amino-acids. The villi are widely different and are unsuited to the absorption of nutrient material.

The bacterial contents of the large intestines may play a part in digesting certain materials which are resistant to the action of the digestive juices in the small intestines, e.g., cellulose, but this digestion is very insignificant in human beings.

Absorption of proteins. Some observers have stated as a result of comparative study of the nitrogenous metabolism in patients on rectal feeding, that quite large amounts of protein are absorbed. Recent observations have, however, demonstrated that this statement was based on fallacious experimentation and cannot be taken at its face value. Boyd has shown that nitrogenous equilibrium could not be obtained during rectal feeding even in those who were accustomed to a diet poor in nitrogen. Laidlaw and Ryffel estimated the nitrogenous output in a case of rectal feeding during coma, and found that it was approximately equal to that obtained in the later stages of fasting, indicating that protein absorption was not taking place. The nutrient enemata they employed, consisted of the white of nine eggs, 6 ounces of raw starch and 24 ounces of peptonised milk in the day. Langdon Brown has carried out a number of experiments by giving nutrient enemata consisting of milk, plasmon, dextrose, sodium bicarbonate and liquor pancreaticus. He estimated the nitrogenous output in the urine, as this is a more accurate criterion of the absorption of nitrogenous material from the bowel than the loss of nitrogen from the rectal washings, which method was employed by previous workers. It was found that the nitrogenous metabolism was hardly affected.

Absorption of carbohydrates. Normally, carbohydrates are absorbed by the bowel as dextrose, and of all the foodstuffs, this appears to be very well utilised in rectal administration. That dextrose is definitely absorbed from the bowel is proved by the fact that the respiratory quotient was raised and that ketosis could be definitely abolished. Mutch and Ryffel advise 6 per cent. of dextrose in 15 ounces of tap water, six hourly, with daily irrigation of the bowel four hours after the last dose. Different observers have claimed that nearly 67 to 100 per cent. of the carbohydrates are absorbed.

Absorption of fats. As is well known, fats are never absorbed *in toto* but are first broken up into glycerin and fatty acids through the agency of an enzyme 'lipase.' This ferment is not present in the large intestines but is supplied by the pancreatic juice. Bacterial decomposition may, under exceptional circumstances, break up the fats but this is not of much significance. Even if the pancreatic ferment is provided by the addition of liquor pancreaticus, absorption of fats is not satisfactory. The fat in the yolk of the egg is considered to be better

absorbed than other forms of fat and has been widely employed. Eggs are, however, not absorbed and most of them are thrown out and add to the nursing difficulties without any advantage to the patient. Though the earlier reports indicate that partial absorption of fats takes place, recent observations by Langdon Brown definitely negative the suggestion. Practically no fat is absorbed from nutrient enemata by the large bowel.

Absorption of salt and water. It is agreed by all physiologists that salts and water are freely absorbed from the large intestines and the advantages claimed for rectal feeding are probably due to these ingredients. It is well known that the body can stand deprivation of food for a considerable time if these articles are supplied. W. Pashev advocated the administration of 10 oz. enemata of plain water at a temperature of 100°F. every four or six hours. Sharkey has used $\frac{1}{2}$ pint of saline four times in each 24 hours with satisfactory results.

It will, therefore, be seen that the principle of rectal feeding is physiologically not very sound. It is only a poor substitute for oral feeding, as absorption from the small intestine is completely cut off. It has been claimed that the larger enemata will get through the ileo-cæcal valve, and be absorbed in the small intestine. Church noted in a case of duodenal fistula that some quantity of a soap and water enema reappeared through the opening. This regurgitation of rectal enemata is such an exceptional circumstance that no reliance can be placed on it. We have, therefore, to depend on the capacity of the rectal mucous membrane to absorb the foodstuffs. As the large intestine is the principal place for the absorption of water, it is essential to supply the nourishment desired, in fluid form. But even in this form, its utility is limited. If any protein is absorbed from the ordinary nutrient enemata, the amount is so small as to make it hardly worth while to subject patients to so much discomfort for so small an advantage. A gain in weight has been claimed as evidence of their value, but this has been observed with rectal salines alone. Eggs and other fatty foods have been shown not to be absorbed. If dextrose is added, ketosis can be definitely stopped and therefore carbohydrates in such forms are the only foodstuff indicated.

It appears possible that better results might be obtained if the proteins are completely broken down into amino-acids, the form in which absorption normally occurs. Rendle Short and Bywaters have found, by allowing pancreatic extract to act on milk for twenty-four hours and using the digested material as an enema, that decidedly better absorption takes place. This plan is worthy of trial in exceptional cases, though its value has not been established beyond doubt.

Disadvantages of rectal feeding. It is true that water, salts and dextrose can be absorbed from the large bowel in sufficient quantities to tide the patient over periods of difficulty and may avoid ketosis when

for some reason or other, the patient cannot take anything by the mouth. There are, however, certain disadvantages which should be borne in mind. Apart from the inconvenience and difficulty caused in keeping the patient in a clean condition, there are certain symptoms which require attention. Excessive thirst, persistent vomiting, reflex secretion of gastric juice, parotitis due to ascending infection of the salivary ducts, etc., are some of the unpleasant complications. These can be avoided to a large extent if proper nursing facilities are available.

3. Administration of drugs by injection. This method is of comparatively recent origin, but its use is being more and more extended every year.

Irritant drugs should not be given by injection into the tissues, as this may cause great pain and swelling and sometimes suppuration, even when all precautions regarding sterilisation are taken, *e.g.*, turpentine, and digitalis glucoside. The advantages of the injection method are :—

(1) Certainty of action, as all the drug gets into the tissues and therefore the dose is definite.

(2) Rapidity of action, as the drug quickly reaches the circulation.

(3) When administration by the mouth is not possible, as when the patient cannot swallow (unconsciousness, drunkenness, etc.) or when the alimentary tract cannot tolerate or absorb drugs (uncontrollable vomiting and diarrhoea).

The disadvantages are :—(1) Abscess may form at the site of injection if precautions are not taken, (2) the drug may be injected by mistake into a vein with disastrous results, (3) the drug may be injected into a nerve giving rise to excruciating pain or paralysis (*e.g.*, quinine). All these can be avoided if sufficient care is taken.

Subcutaneous or hypodermic injection. In this method, the drug is given into the subcutaneous tissues by means of a hollow needle. All preparations meant for subcutaneous injection should be in liquid form, solutions or colloidal suspensions should be capable of complete absorption, for otherwise they will set up irritation. The quantity injected should not be too large (under 5 c.cm). Large quantities of saline are sometimes injected into the loose tissue about the

breast, axilla, abdomen or into the back below the scapulæ, the liquid being allowed to run in slowly. Care should be taken that the fluid is isotonic or nearly so with blood, for otherwise it will not be absorbed and pressure on vessels may cause gangrene or abscess.

Subdural injections. These are used when the drug is required to act directly on the spinal cord and nerve roots, *e.g.*, spinal anaesthesia. Colloidal drugs, which do not readily permeate the nervous tissue from the blood, are also given by this way, *e.g.*, tetanus antitoxin. The technique is that of lumbar puncture, some cerebro-spinal fluid being withdrawn before the injection is made. The procedure is dangerous if the drug produces local irritation or is conveyed to the medulla and thus acts on the vital centres. The absorption of drugs from subdural injection into the general circulation is doubtful, as even drugs like adrenalin, nicotine, etc., do not produce their general effects. During intra-spinal administration the patient should keep in a rigidly fixed position, otherwise the movement of the patient may break the needle, which is a very serious matter. Sub-arachnoid irrigation has been experimentally tried.

Intracranial administration is sometimes given in urgent cases, and drugs like salvarsan have been given through a trephine hole in the skull. Special training and technique is necessary for both these.

Sub-lingual and sub-nasal administration. Injections under the mucous membrane in these regions are rapidly absorbed, being as effective as intravenous injections. Some drugs like nitroglycerin can be given effectively by holding a tablet under the tongue.

Intrapericardial injections. Solutions are rapidly absorbed from the pericardium into the heart muscle. It has been suggested that this method may be used for epinephrine resuscitation in extreme cases. Intracardiac injection is now employed for this purpose.

Intraperitoneal and intrapleural injections. These are used in animal experimentation, but rarely in man. The pleura absorbs from the parietal and pulmonary surfaces, but the absorption is less from the peritoneum. In both cases the absorption occurs by the blood stream rather than by the lymph. Gravity plays a part, the absorption being little from the pelvis.

Intrahepatic injections. These are used instead of intravenous injections in small animals, such as frogs, turtles and rats, but are not recommended in man.

Intramuscular injections. These are made by thrusting the needle through the skin deep into the substance of the gluteal or other muscles. The injections do not remain confined to the muscle, but rupture the muscle bundles and spread

along the nearest fasciæ, thus greatly increasing the absorbing surface. The absorption, therefore, is more rapid than with subcutaneous administration and in view of the fact that sensory nerve-endings are fewer than in the skin, the pain is less evident. The tendency to abscess formation is also much less. Intramuscular injections are particularly useful when relatively insoluble powders suspended in oil have to be administered. These establish a depot for gradual absorption and continued action, *e.g.*, mercury salicylate in the treatment of syphilis. Suspension of metallic salts in oil are best injected intramuscularly as they are not absorbed from the subcutaneous tissues.

Intravenous administration. During recent years, the practice of intravenous medication has come to the forefront. Twenty years ago, medical men would not willingly undertake the injection of a drug into a vein. Now-a-days, however, the popularity of the method has increased and the modern physician performs this operation with alacrity and skill. Attempt is made to give almost every drug by this route on the assumption that intravenous medication produces a more powerful therapeutic effects than administration of drugs by other channels. This misconception has assumed such proportions that it is both timely and important to consider the real merits and limitations of this form of therapy.

Evolution of the method. The idea of intravenous medication was first started in 1655 when Christopher Wren experimented on dogs and showed that drugs could be given into a vein without ill-effects. A year later the first intravenous injection was given in man. Later, others tried this method of medication with a variety of drugs, but the haphazard ways of experimentation damaged the reputation of this procedure. Bacelli (1890) saved the method from adverse criticisms by his successful treatment of malaria with intravenous quinine. He advocated the method as a routine treatment on the assumption that the drug was brought immediately into contact with the parasites whereas when given by the oral route the time required for absorption would necessarily delay action. His support of intravenous therapy, at a time when the method was almost being discarded as dangerous, had a very steadying effect on the minds of medical men and since then, the method has gradually gained in popularity. Crede (1902) tried colloidal metals in the treatment of

septicaemia, but his attempts were not successful, as several fatalities occurred. The discovery of salvarsan in the beginning of this century and its safe intravenous use put intravenous therapy on a sound and stable basis (1910). The demonstration of the relative harmlessness of intravenous salvarsan injection came as a great relief to the physician who could thus treat syphilis without giving the patient the excruciating pain attending on intramuscular injections.

Physiological considerations. A knowledge of the inherent properties of the blood is essential in order to have a closer conception of this method of administration. A brief reference to the physiological considerations will not, therefore, be out of place here.

The blood is the chief medium through which any drug introduced by any channel will be distributed to different parts of the body. It is a special fluid, having the function of carrying nutrition and oxygen to all the tissues and eliminating the waste products that accumulate as a result of metabolism. It also takes certain chemical substances that are formed by physiological activity of an organ to other organs, thus regulating and co-ordinating the functions of different organs of the body. The total volume of blood has been estimated approximately to be $1/13$ of the body weight. The erythrocytes form about 50 per cent. of the total mass and consist of two parts, stroma and haemoglobin in a state of loose combination. This combination may be broken up by various means such as dilution of the blood with water, addition of ether, or bringing it into contact with haemolysins. Laking of the blood by dilution with water makes the consideration of the osmotic relations of the erythrocytes an important study in intravenous injection. If the osmotic pressure of the blood plasma is reduced by diluting with water, the corpuscles in order to maintain the balance, break up liberating their haemoglobin. If a strong solution of common salt is added to the blood so as to make the osmotic pressure of the plasma higher than that of the erythrocytes, water will pass from the corpuscles to the plasma to maintain the equilibrium and the corpuscles will be crenated. The osmotic pressure of both the plasma and the corpuscle will, therefore, remain unaffected between these two extremes and this point is reached by a solution containing 0.9 per cent. of sodium chloride, for mammalian blood. The erythrocytes are impermeable to most neutral salts and, therefore, it is possible to make normal solutions with sodium sulphate or with cane sugar by making the solution isotonic with 0.9 per cent. sodium chloride. Certain substances like alcohol, ether, etc., however, can permeate through the corpuscles. The blood corpuscles resemble most animal and vegetable cells in permitting the passage of those substances that are soluble in fat and fat-like bodies, e.g., lecithin and cholestrin.

(a) **Specific gravity of blood.** The specific gravity of the blood in the male sex varies between 1055 and 1058 and in the female sex from

1054 to 1056. The question of specific gravity becomes important when large quantities of saline are infused intravenously as in cases of cholera. If the specific gravity of the blood is high enough, as it is in this disease, very large quantities of saline can be injected without any untoward effects. When the specific gravity is within normal limits, administration of large quantities of saline is liable to produce oedema of lungs and death.

(b) **Hydrogen-ion-concentration.** The hydrogen-ion-concentration of the blood is another important consideration in intravenous therapy. The blood, as is well known, is alkaline to litmus. The pH of this fluid depends mainly upon the ratio between the concentration of carbon dioxide and bicarbonates in the blood, and these two are so balanced that the pH is just on the alkaline side of neutrality. This balance may be expressed as an equation: $H \text{ (hydrogen-ion-concentration)} = K \cdot \frac{H_2CO_3}{NaHCO_3}$, where K is a constant. An addition of a trace of acid or alkali will disturb the balance by increasing or decreasing its numerator or denominator and make the pH move towards the acid or alkaline side of neutrality. The tissues and especially the higher centres in the medulla are extremely sensitive to the slightest changes in the hydrogen-ion-concentration of the blood, and any change in the relative proportions of H and OH ions which will take the pH of the blood to the acid side of neutrality will be met with rapid fatal results. Under ordinary conditions, therefore, intravenous injection of any acid solution would have been impossible. The blood, however, contains certain substances called 'buffers' which play an important part in maintaining the pH of the blood at a constant level. The mechanism by which the neutrality of the blood is maintained is described in detail in chapter on acidosis and alkalosis.

The balance of pH is so delicately maintained, that ordinary injection of drugs which are distinctly acid or alkaline produce no permanent change in the reaction of the blood. If, however, the rate of injection is rapid, the buffers present may not be able to keep the balance intact.

(c) **Volume of the blood.** The volume of the blood is another important subject for detailed study in connection with intravenous therapy. It is a well-known fact that the blood volume remains fairly constant despite influences which tend to alter it. After a severe hæmorrhage, the volume of the blood is made up by gradual imbibition of fluid from the tissues. Again when large quantities of saline solutions are injected into the circulation, the total blood volume does not alter permanently. In animals, about 100 to 200 c.cm. of normal saline infused slowly do not produce a rise in arterial pressure proportionate to the quantity injected. The fluid, therefore, must be accommodated either inside or outside the vascular system. There may be dilatation of the arterioles and capillaries to make room for the extra

volume of fluid or the fluid may pass out of the circulation into the tissues as lymph. Both factors appear to operate simultaneously. Immediately after such a transfusion an increased fullness in the vessels of the mucous membrane and retina can be observed. The fluid portions of the blood, however, rapidly pass from the blood vessels to the tissues giving rise to œdema, if the quantity of the fluid transfused is very large. This œdema might set in in such vital organs as the lungs and may produce serious respiratory distress or even death.

(d) **Air-embolism.** The question of the entry of air into the circulation may be briefly reviewed here. It is a matter of common observation in laboratories that small quantities of air introduced into the circulation do not have any deleterious effect on an animal. On the other hand, injection of large quantities of air is the quickest and surest method of killing an animal; 5 c.cm. of air suddenly introduced into the vein of a rabbit will produce fatal results within 2 or 3 minutes. If, however, the air is introduced slowly the animal does not die. If 5 to 10 c.cm. of air are injected abruptly into the vein of a cat, an immediate fall in blood pressure to zero is produced. The churning of blood and air in the heart produces froth, and sudden heart failure may occur due to very small quantities of blood entering the coronary arteries with consequent impairment of the nutrition of the heart. It must be realised, however, that in order to produce such result in man, the quantity of air introduced must be very large. Five to 10 c.cm. of air, even when introduced suddenly, will be rapidly absorbed by the blood and will produce no deleterious effects whatsoever.

Choice of drugs for injection. The selection of the salt to be given when several salts of an alkaloid are available should depend upon the solubility of the salt and its rate of diffusibility. Generally, the hydrochlorides are more soluble and more diffusible than the sulphates because of the smaller size of their molecules. Another point in favour of hydrochlorides is that HCl combines with the calcium of the blood, forming calcium chloride which is soluble. The calcium content of the blood will, therefore, not be affected. If a sulphate is given, the insoluble calcium sulphate which is produced will be precipitated and will deprive the heart of its proper calcium requirements. The chemical changes, such as these occurring in the blood, however, are so insignificant with ordinary injections that their effects are negligible in view of the large volume of the blood in circulation.

Some salts such as the pentavalent compounds of antimony produce a precipitate in the blood. This precipitate may

produce respiratory distress but the symptoms pass off rapidly and generally produce no untoward effects. Substances like salvarsan are not soluble in neutral watery solutions and therefore the blood cannot hold them in complete solution. They circulate in the blood in a semi-colloidal state.

Indications. The following are some of the chief indications for the administration of drugs by the intravenous route.

1. As an emergency measure when rapidity of action is desirable. A few examples may be given to illustrate the point:—(a) For combating acidosis in the body, *e.g.*, in diabetic coma, the intravenous infusion of saline, sodium bicarbonate, insulin, etc., may save the patient's life. (b) In severe forms of tetany, intravenous injections of calcium may prevent death. (c) In auricular fibrillation with impending death, an intravenous injection of strophanthin may act like a charm. (d) In malignant malaria, intravenous administration of quinine produces rapid curative effects. (e) Neglected and severe cases of diphtheria often demand the intravenous use of antitoxin, and sometimes respond to it favourably.

2. When greater intensity of action is desired than can be secured by other methods of administration. Arsenicals are given in syphilis by this route to produce an effective concentration in the blood. Antitetanic, antimeningococcic and antistreptococcic sera (especially for scarlet fever) are sometimes given intravenously to produce stronger action than can be obtained when given subcutaneously. Non-specific proteins, when used to induce protein shock, are best given into the vein, *e.g.*, typhoid vaccine in chronic arthritis.

3. To secure direct action on the infecting organisms within the blood stream, *e.g.*, quinine in malignant malaria, mercurochrome 220 soluble, gentian violet and colloidal metals in septicaemia.

4. To avoid irritation and destruction of tissue likely to be produced by drugs, such as arsenicals and antimonials, when given by other routes.

5. When the volume of the fluid is large it is better to give it intravenously than intramuscularly or subcutaneously, *e.g.*, injections of saline in cholera. Though large quantities

of saline can be given under the breast and in the loose areolar tissues of the axilla, the procedure is very painful and should be avoided as far as possible.

Advantages over other modes of administration. 1. Precision of dosage. This can only be attained by injecting a drug straight into the blood stream. There is no certainty what amount of a drug administered orally is going to be absorbed finally into the circulation.

2. Absence of gastro-intestinal irritation: Arsenicals and antimonials cannot be given by the mouth.

3. Stability of the drug, *e.g.*, adrenaline and many hormones are rendered inert when given by the oral route.

4. Prompt action.

5. Avoiding irritation or destruction of tissue when given by subcutaneous or intramuscular method. •

Disadvantages and contra-indications. Intravenous medication should not be resorted to if a drug can be effectively given by any of the other routes, as there are many risks attached to this form of medication. There is a growing tendency on the part of medical practitioners to resort to intravenous injections when the utility of this method is doubtful. This is to be strongly deprecated. The injection of foreign substances into the blood stream should always be considered a serious undertaking and the advantages and disadvantages should be carefully weighed before it is actually practised. The risks of intravenous injection frequently outweigh its probable benefits in (a) greatly debilitated patients, (b) the aged, (c) patients with hypertension and arteriosclerosis, (d) patients suspected of being subject to anaphylactic reactions, *e.g.*, asthma, urticaria, sensitiveness to drugs. Furthermore, the injection of substances likely to disturb or produce a subversion of the delicate physiological balance of the blood is contra-indicated. Substances markedly acid or alkaline in reaction, imperfectly purified substances, substances which do not dissolve in water, haemolytic agents, emulsions of fats and oils set up untoward effects which may be serious.

Technique of intravenous injection. The best veins to choose are those at the bend of the elbow, but if the patient is well covered these veins may be buried in fat and it may be easier to puncture one of the veins on the back of the hand. The latter are very moveable and it is often very difficult to puncture the vein, even when the needle is through the skin, as it recedes in front of the advancing needle and then suddenly slips away from it. There is a large vein at the back of the wrist running over the outer side of the head of the radius between the tendons of the extensor carpi radialis longus and of the extensor pollicis brevis which is extremely useful, especially in children, in whom it is often as big as the little finger. The vein is not usually blue but can very easily be felt, and if congestion is caused it will stand out very prominently. The disadvantages in using this vein are that the skin over it is usually tough and there is a nerve just under it which may be accidentally injured.

The skin over the vein should be sterilised with alcohol. If iodine is used it must be washed off with alcohol, otherwise it will increase the difficulty of seeing the vein. Washing the skin with xylol will increase the visibility of the veins but this is seldom necessary. Engorgement is caused by putting a rubber ligature round the arm above the point at which the vein is to be punctured. This ligature must be tight enough to stop the venous return but not tight enough to stop the arterial flow to the limb. Further congestion may be caused by gentle upward massage or by rapid extensor and flexor movements of the limb by the patient. The patient should be either lying down or sitting at a table with the elbow on a small pillow. The syringe should be held in the right hand at an angle of about fifteen degrees with the skin surface and entered upwards and along the long axis of the vein. The point may enter the vein immediately or the vein may slip to one side; in the latter case the point of the needle must be made to follow the vein, pressing into the side of the vein until it is pierced. Directly the vein is punctured, blood will enter into the barrel of the syringe, which has been previously loaded with the dose that is to be injected. The congesting band is now released and the solution slowly injected. The injections should in all cases be given as slowly as possible; not less than two full minutes should be taken over the injection of a maximum dose. When once the point of the needle is in the lumen of the vein, every effort must be made to prevent its either slipping out again or being pushed through the opposite wall of the vein. During the loosening of the constriction and the pressing home of the plunger the operating hand must be steadied by being rested on the arm of the patient. If at any time during the operation there is any doubt as to whether the point is within the lumen of the vein, the operator can satisfy himself by slightly withdrawing the plunger again. If the needle is still in position

blood will again flow into the syringe. Great care must be taken that no air escapes into the vein from the syringe.

The syringe that is used must be all glass or glass and metal. The smaller the syringe, the easier it will be to give the injection. A 5 c.cm. syringe will generally be found the most useful one for this purpose.

In children, who are very likely to wriggle during the operation, a good method is to hold the syringe in the right hand and with the left hand grip the arm so that the back of the elbow lies in the hollow of the hand and the first two fingers and the thumb can be approximated in front of the elbow; as the needle is passed into the vein the barrel of the syringe is gripped between the fingers and thumb of the left hand so that the syringe and the arm cannot possibly move independently. It will not be found necessary to grip so tightly that the venous flow is stopped.

The drugs used must be of established purity determined by chemical or biological methods and should be freely soluble in ordinary solvents. Substances which are imperfectly soluble should on no account be injected into the vein unless they are in a colloidal state.

The solution. (a) The water used for the solution of the agent to be injected must always be freshly distilled. Ordinary commercial distilled waters should be avoided, if possible, as they are liable to produce rigors and temperature. Besides, there is every chance of ordinary distilled water turning acid immediately after distillation, owing chiefly to the absorption of CO_2 from the atmosphere.

(b) Sterility of the solution just before injection is essential. This may be attained by autoclaving the solution if there is no chance of the drug breaking up by heat.

(c) The possibility of decomposition of the solution should be borne in mind. Heat converts a part of NaHCO_3 into a much more caustic and alkaline carbonate. Such substances as strophanthin are decomposed when their solutions are put up in soft glass ampoules, owing to the liberation of alkali from the glass. The physician should see if hard glass has been used for such ampoules before giving the injection.

(d) The reaction of the solution is important. All solutions for intravenous use should conform as closely as possible to the reaction of the normal blood which is slightly on the alkaline side of neutrality (pH 7.4).

(e) Solutions should always be as nearly isotonic with the blood as possible whenever the volume of fluid to be injected is large. Exception to this are conditions such as cholera and high intracranial pressure, when hypertonic solutions are necessary.

(f) The rate of injection of the solution should be slow in order that the circulation is not overwhelmed with large volumes of the fluid which it cannot cope with rapidly. Injection at a slow rate is specially

important in connection with potent drugs like arsenicals, and antimonials.

(g) The temperature of the solution should be approximately that of the body, otherwise unpleasant reactions might result.

Reactions and dangers. There are various risks attendant on intravenous therapy and in order to avoid them, those using the method should thoroughly familiarize themselves with the details of the technique. When it is realised how well the equilibrium in the blood is maintained, the grave consequences of its disturbance, the relative ease with which it may be upset and the serious accidents which may follow, will be obvious.

Dangers from the solution used. Anaphylactoid phenomena evidenced by rigors, chill, vomiting, sweating and pyrexia. Rigors and fever may follow immediately after intravenous injection, especially if large volumes of substances like saline or glucose are given. Such reactions are very disturbing and their real nature is not clear. Seibert (1925) showed that distilled water frequently contains a pyrogenous body which is the product of its contamination with living organisms. This pyrogen is produced by the growth of the organisms and is not present in freshly distilled water. The water used should therefore be freshly distilled, unless it is properly preserved. The other view is that the anaphylactic reactions are the result of physico-chemical disturbances in the plasma set up by rapid changes in the blood. The temperature of the fluid at the time of its entrance into the vein is also important. It should be realised that the temperature of the solution in the funnel or glass barrel used in the gravity method is not the same as that at the tip of the needle, for the solution cools down during its passage through the rubber tubing.

Danger from the agent employed. No agent should be used for intravenous injection which has got any deleterious effect on the circulation and is therefore likely to produce dangerous reactions. Rendle Short has described a dangerous condition from the intravenous use of sodium chloride in large quantities. If the total quantity injected is very large—10 gm. or more—a condition of 'hydræmic plethora' is likely to be induced by dilution and increase in the total volume of the blood.

It has also been shown that the specific gravity falls from 1064 to 1054 after an injection; the kidneys and lymph channels promptly excrete the excess of fluid and may overshoot the mark, so that eventually the specific gravity may rise to 1067; the total blood is less in bulk and even more concentrated than it was before. This does not occur if the supply of fluid is kept up by administering saline per rectum.

If the kidneys are not capable of excreting water and salt quickly enough, there will be water-logging and some degree of dropsy may occur. This may take the form of fatal œdema of the lungs. This danger has frequently been met with following saline transfusion, especially in patients with nephritis.

Thrombosis and embolism. These conditions have frequently been mentioned as the most dangerous outcome of intravenous therapy, and numerous instances of death following thrombosis and embolism of the pulmonary capillaries have been recorded. It is possible that sudden death might follow intravascular clotting and an embolus might stop the heart at any moment by blocking the coronary arteries. But serious results attributable to thrombosis or embolism are seldom met with in practice and one or two bubbles of air injected with the solution in the syringe do not produce 'air embolism.' Nevertheless there is a chance of thrombosis starting at the site of injection, if the agent injected is sufficiently irritant to cause damage to the endothelial lining of the vein. To prevent this, an additional quantity of saline should be injected to wash down the irritant drug. This is the usual practice with drugs like salvarsan.

Associated dangers. These are not directly due to the injection but are the results of faulty technique, occurring especially with those who are not experienced in the art of intravenous injection. The injection of drugs like arsenic, antimony, calcium and iodine, in the perivascular tissues is fraught with serious results in the shape of acute inflammation and abscess formation requiring surgical intervention. Fibrosis (local) leading to limitation of movement of the elbow joint is not an unusual complication. Tetanus is also known to have occurred as a result of injection with imperfectly sterilised

syringe and needle or improper attention to sterilisation of skin. All these dangers can be prevented with proper care and attention on the part of medical practitioners.

INTRAVENOUS THERAPY

A host of drugs are now being used in intravenous therapy and an enumeration of all these preparations is not necessary. The list of such drugs has been rapidly growing of late years with the introduction of new remedies, mostly the outcome of chemotherapeutic research. A systematic account of all these drugs is difficult, for all of them have not been studied with sufficient thoroughness. The important drugs in use can be classified as follows:—

1. Substances that bring about a change in the blood condition.

(a) Change in volume—saline, glucose, blood transfusion, etc.

(b) Change in reaction—sodium bicarbonate.

(c) Change in coagulability—calcium chloride.

2. Specific agents against protozoal organisms—cinchona alkaloids, emetine, compounds of antimony, arsenic and mercury.

3. Agents used against bacterial organisms—dyes, iodine, hexamine.

4. Immunity-producing agents,—sera, vaccines.

5. Anaesthetic agents—hedonal, magnesium sulphate, evipan-sodium.

6. Agents that cause sclerosis of the veins—phenol, etc.

7. Diagnostic agents—uroselectan B, sodium-tetra-iodo-phenolphthalein.

1. SUBSTANCES THAT BRING ABOUT A CHANGE IN THE BLOOD CONDITION

Intravenous saline infusion. Intravenous administration of saline solution is attended with such marvellous results that it is considered as one of the triumphs of intravenous therapy. Its application has come to the forefront in the treatment of wound shock during the recent

War. The successful application of saline in the treatment of cholera has made it the most popular remedy. Every medical man in the tropics should, therefore, be familiar with the technique of injection.

The chief indications for intravenous saline infusion are: (a) To increase blood volume, (b) to combat toxæmia and (c) to effect dehydration.

(a) Intravenous injection of saline is pre-eminently indicated in conditions of surgical shock. This condition is characterised by a fall in blood pressure and paralysis of the capillaries, so that all the blood in the circulation accumulates in the splanchnic area. The heart does not get sufficient blood to pump into the systemic circulation and the higher centres of the brain suffer. In this condition, a saline infusion by restoring the failing circulation, might prove of immense benefit to the patient. Sometimes, however, the results of a saline transfusion are disappointing, owing possibly to increased capillary permeability which permits fluids, salts and even plasma proteins to leak out of the blood vessels into the tissues. To combat this difficulty, Bayliss, during the Great War resorted to colloidal solutions containing gum acacia. Such solutions were apparently more effectively retained than simple chloride solutions and the procedure was considered life-saving in many instances. Bayliss claimed that by this means disastrous results can be prevented even when the blood corpuscles are reduced to half their original number, a reduction otherwise fatal. As acacia is a colloid and the blood vessels are impermeable to colloids, it attracts or retains water in the blood. Doubts have, however, been expressed regarding the safety and efficacy of this procedure. Hanzlik and his collaborators found intravenous injection of gum acacia solutions harmful and dangerous. These dangers could probably be avoided by greater care in the selection of the gum used and the preparation of the solutions. This form of therapy has not been used much during recent years.

Intravenous saline infusion is again the best form of treatment in cholera. Cholera is characterised by excessive vomiting and purging, and consequently there is tremendous loss of water from the system. The blood becomes thick and the specific gravity rises; in fact, dehydration may be so marked that the delicate cells of the body suffer serious injury from water starvation. If at this juncture, the fluid loss is compensated by liberal quantities of saline solution, the crisis can be avoided in most cases. A good deal of care is necessary to determine the amount of saline to be injected. An excessive quantity of saline introduced into the circulation at a rapid rate may give rise to oedema of the lungs and right heart failure in certain cases. A simple way suggested for avoiding these difficulties is to introduce the saline after determining the specific gravity of the blood. A litre of normal saline for every unit rise of specific gravity above 1060 is considered a safe quantity, provided no other complications are present.

The disadvantage of normal saline is that it passes out of the circulation very quickly and the improvement obtained is short-lived. As in cases of surgical shock, Bayliss' gum saline transfusion is not particularly advantageous, as the aim of treatment in cases of cholera is to antagonise the tissue thirst rather than to increase the blood volume through the agency of a non-diffusible colloid. Rogers successfully used hypertonic saline containing 120 grains of sodium chloride to one pint of water. This procedure obviates the necessity of frequent repetition of injection to keep up the blood volume, as a hypertonic solution does not pass out of the circulation as quickly as normal saline.

(b) Saline solutions are administered intravenously to combat various forms of toxæmia. The toxæmia resulting from high intestinal obstruction and stasis is associated with marked dehydration and concentration of the blood. Here, a litre of a 1.0 per cent. solution of sodium chloride is given intravenously two to three times a day, with striking improvement. Similar gratifying results after saline infusions are also obtained in cases of gastro-jejunostomy and cholecystectomy where toxæmic symptoms have supervened after operation. After excessive burns and gas poisoning the tissues suffer from marked dehydration, and in these conditions intravenous saline infusions have sometimes been of remarkable utility.

(c) Of late years, intravenous injections of hypertonic saline solutions have been largely used for reduction of increased intracranial tension. This is important in brain surgery and the procedure has made many operations on the cerebrum possible, which otherwise could not have been attempted for fear of causing post operative hernia of the meninges. It has been pointed out that it is possible to diminish the intracranial pressure by the injection of a 35 per cent. solution of sodium chloride into the blood stream and that this is accompanied by a reduction in the cerebro-spinal fluid pressure. Malone has successfully used a strong salt solution to control excessive intra-cranial tension and for the relief of 'tension headaches,' such as may occur in persons suffering from cerebral tumours. The effects appear to be due to the osmotic pressure of hypertonic solutions which causes withdrawal of fluid from the tissues generally, and probably also decreases the formation of cerebro-spinal fluid.

Intravenous Glucose

The intravenous administration of glucose solution has now attained a position of considerable importance as a rational therapeutic measure in general medicine, obstetrics and surgery. It is difficult to enumerate the various pathological states for which glucose has been utilised with benefit. As a nutrient

in undernutrition, it has been widely employed. It was originally employed for its diuretic action. Many people use it for the combined purposes of nutrition and prevention of acidosis in patients suffering from vomiting or shock or in gastro-intestinal disorders.

Dosage. The average dose for an adult is about one gm. per kilogram of body weight. An average adult weighs between 50 and 75 kg. so that 75 gm. can be given as the initial dose, subsequent doses being 50 gm.

Solvent. The glucose given by this route should be chemically pure and should be dissolved in freshly double-distilled, uncontaminated water and not in salt solution or sodium bicarbonate solution, as has been sometimes recommended. In the preparation of a single dose, 50 gm. of the glucose is carefully weighed and then dissolved in 200 c.cm. of freshly distilled water, using only glassware which has been thoroughly washed in distilled water. Before sterilisation the solution should be filtered at least five or six times to remove tiny particles of dust or cotton fibres. For the sake of simplicity in making any necessary calculations for dilutions it is convenient to have each flask contain 25 gm. of glucose in 100 c.cm. of water (25 per cent.) or a half dose.

Fresh double-distilled water is used for preparing glucose solution for intravenous injections and as a diluent of the more concentrated solutions in ampoules now on the market.

Concentration of solution. A 25 per cent. solution (50 gm. in 200 c. cm. of water) is the generally desirable strength. A 6 per cent. solution was at first used, but the concentration has been gradually increased up to this point, as the direct result of the observation that the stronger the solution the more rapid and lasting are the effects. Moreover, some extremely unpleasant consequences have followed in some instances, notably in pneumonia, when the vascular system has been rapidly overloaded by a large volume of weak glucose solution. It is apparent that if the solution is weak a large amount must be given in order to carry a therapeutic dose of the glucose. It is, we believe, a distinct advantage to use a strongly hypertonic solution because its hypertonicity actually favours a more rapid inter-change between the tissues and the blood stream, so that toxins are diluted, oedema lessened, and the sugar seized and stored more rapidly by the tissues.

If more fluid is required by the body, it is safer to consider this as an entirely separate matter and administer it as sub-mammary infusions of salt or weak glucose solution.

A ten per cent. solution of glucose should be considered as about the lowest limit of safety in dilution and a 25 per cent. solution should be preferred unless there is some definite indication for immediate and rapid administration of additional fluid by the blood stream route. It is quite likely that certain reactions are attributable to injection of an excess of distilled water when weaker solutions are used.

Sterilisation. The flasks of glucose solution after being properly stoppered with cotton plugs in gauze and the top sealed with lead foil, should be sterilised in a steam steriliser for one-half hour at 100°C. on three successive days. It may be prepared more quickly for emergencies by being sterilised in an autoclave at 15 pounds pressure for twenty minutes. In either case sufficient space should be left between the level of the solution in the flask and the stopper so that the solution will not be forced by vacuum up against the stopper. This is also a precautionary measure against the possibility of splashing the solution against the stopper in any handling of the flasks.

Solutions showing caramelization or sediment after sterilisation should be discarded.

Age of solution. Glucose solutions kept in flasks stoppered with cotton, or cotton and gauze, and sealed with lead foil will show comparatively little change in hydrogen-ion-concentration over a considerable period of time, even though buffer salts have not been added, so that solutions may be prepared in advance of the need for them. Flasks of glucose solution kept on a laboratory shelf for six months showed practically no change in acidity. As a matter of fact, the greatest variation takes place during the course of the sterilisation of the solution and from then onwards it remains fairly constant.

Solutions should preferably not be kept longer than four weeks unless hermetically sealed, and the fresher the solution

the safer it probably is. Reactions can rarely be traced to those solutions that are not older than two to four weeks.

Ampoules of glucose solution:—Ampoules of glucose (dextrose) solution are now on the market and have been carefully and properly prepared by manufacturers. Those containing preservatives should be avoided.

Hospitals which are using large amounts of glucose intravenously find it economical to prepare their own solutions, but for small services or emergency work these ampoules are very useful. For convenience and compactness they are usually prepared as 50 per cent. solutions (25 gm. of glucose in 50 c.cm. of water) with directions for diluting. If freshly distilled sterilised water cannot be obtained for this purpose, it is probably safer to inject the solution as it comes from the ampoule even though so highly concentrated.

Technique of administration:—An individual can utilise only 0.8 gm. per kilo. of body weight per hour of injected glucose and to give more than this amount by too rapid a rate of injection results in its immediate excretion through the urine. Calculating from the rate of utilisation, the injection should be given slowly at the rate of 4 c.cm. per minute for a 25 per cent. solution, and during this period the solution should be kept warm. The solution is ordinarily injected from a salvarsan tube, using a small calibre needle, and having the tube coiled in a basin of hot water to keep the temperature of the flowing fluid from 100° to 110°F.

Fresh rubber tubing should not be used until after it has been thoroughly washed in running water, then boiled in clean water (without sodium carbonate), again washed, and finally sterilised in an autoclave. Chemical contamination from new rubber tubing has been suggested as a cause of reaction following these injections.

The salvarsan tube and the connecting tubes, as well as the rubber tubing, should be thoroughly cleansed and then sterilised in an autoclave because when merely boiled, sediment from water is often to be seen within the glass. Before beginning the injection the system should be rinsed out by running distilled water through the salvarsan tube, the rubber tubing, the connections and the needle.

Blood Transfusion

The method of infusing new blood, from one man or animal into another man, came into being as early as 1650. Since then, it has been practised from time to time but on account of the occurrence of frequent catastrophes it was entirely given up. The method almost received its death-blow at the hands of William Hunter who wrote "For practical purposes all the advantages to be gained from transfusion may be equally well and more readily obtained by infusion of a neutral saline solution of common salt." This utterance, coupled

with the difficulty of technique in performing the operation successfully, kept the method practically out of the therapeutic field until recently (1910) when Moss described the four human blood groups. Since then transfusion has again gained popularity and since the Great War, it has come to be universally recognised as a very useful therapeutic measure.

Indications. These may be classified under four main groups. (1) Acute hæmorrhage and anæmia. (2) Chronic anæmia, to tide the patient over an operation, or to benefit the condition, prolong life and in the hope of cure, *e.g.*, Addisonian anæmia, anæmia of pregnancy, (3) In hæmorrhagic diseases. (4) In general toxæmia of bacterial or chemical origin.

Acute anæmia due to hæmorrhage is most successfully treated by blood transfusion. During the Great War it was amply proved to be a live-saving measure in conditions of traumatic hæmorrhage and shock. Its value in post-partum hæmorrhage and ruptured ectopic gestation has also been widely acknowledged. Blood transfusion is now thought to be superior to transfusion of saline and gum solution. After saline, the patient often improves for some time and then goes down again; after blood transfusion, on the other hand, the immediate benefit may not be striking but the permanent results are ensured. The reason of this is that transfused cells actually carry oxygen to the starved tissue cells, which gum saline cannot do.

In gastro-intestinal hæmorrhage, blood transfusion is distinctly useful and some authorities recommend small repeated transfusions rather than one large one. The fear that by increasing the arterial pressure, transfusion may induce bleeding from the original site of the ulcer seems to be unfounded, for the rise in arterial pressure is never more than 20 mm. of mercury and it is too transient to produce any appreciable effect.

In chronic anæmias due to repeated small hæmorrhages, debility, gynaecological conditions small repeated transfusions of blood have been employed in order to render feasible a surgical operations. Doubts have been expressed as to what extent blood transfusion does good in chronic anæmias. Theoretically, the problem is not so simple as in the case of acute hæmorrhage, for the etiological factors persist and must be taken into account. In Addisonian anæmia, though transfusion has been practised a lot with the idea of supplying healthy blood with its hormones and antibodies so as to stimulate the activity of the bone-marrow, the efficacy of this procedure is doubtful. It is difficult to imagine how anything could stimulate the blood-producing organs which are at fault and if they are stimulated it is probable that abnormal cells, instead of normal red blood cells, may be produced.

In hæmorrhagic diseases. In these diseases, transfusion is beneficial as it supplies the necessary thrombogenic factors, fibrinogen and blood

platelets. If the citrate method of transfusion is used, there is no difficulty in spite of its anticoagulant action.

(i) **Purpura hæmorrhagica** is characterised by bleeding from mucous surfaces, a diminution in the number of blood platelets in the shed blood and a prolonged bleeding time. Repeated blood transfusion was formerly the chief form of treatment but splenectomy is now resorted to.

(ii) **Melæna neonatorum**. Blood transfusion is the only rational and successful treatment. There are technical difficulties in performing blood transfusion in the new-born but if done successfully, one transfusion is sufficient in the majority of cases. Failing this, whole blood may be given intramuscularly.

(iii) **Hæmophilia**. Although the blood platelets are never diminished in this disease, blood transfusion is beneficial both to counteract anæmia and to prevent bleeding during an operation. The hæmostatic effect is supposed to be due to the introduction of fresh blood platelets.

(iv) **Jaundice**. Transfusion has been tried in some cases of severe jaundice with prolonged coagulation time, as a prophylactic measure before surgical operations. The results however are not uniformly successful.

(v) **In black-water fever**. Transfusion of whole blood at the time of or immediately after an attack of fever is a useful therapeutic measure. The fear of causing more hæmolysis should never be allowed to prevent blood transfusion in desperate cases.

General toxæmia—bacterial or chemical. In chronic infections and intoxications, the value of transfusion has been acknowledged. Chronic debilitating conditions associated with malnutrition and marked anæmia have been treated frequently by blood transfusion with gratifying results. These conditions are mostly the outcome of chronic septic absorption from some unknown focus. In sprue, which may be considered to be a disease produced from bacterial intoxication, blood transfusion has often proved beneficial.

In acute toxæmic conditions, the general opinion is against blood transfusion inasmuch as the benefit derived is doubtful and actual harm may follow from the formation of abnormal agglutinins and hæmolysins. It has, however, been thought by some that transfusion may increase the patient's general resistance, possibly because the infused blood may happen to contain specific antibodies. With this idea in view, Wright and his co-workers have advocated the method of *immuno-transfusion* the aim of which is to inject a blood which contains a bactericidal plasma and leucocytes, for both these elements play a rôle in defence. In conditions of acute septicæmia, the leucocytes seem to be paralysed so that the injection of vaccine, which is sufficient to stimulate antibody formation under all other conditions, is of no

avail. Immuno-transfusion under these conditions is said to act like a charm. The immunisation of the donor's blood is accomplished by giving him injections of vaccine, the blood in this way developing exalted bactericidal power. As the aim is to obtain large amounts of non-specific antibodies, the use of staphylococci is permissible and convenient, whatever may be the infecting agent of the patient. The increased hæmo-bactericidal power of the donor's blood is lost after about 48 hours, so the process has to be repeated in order to have a lasting effect.

In poisoning by chemicals such as CO, P, etc., the introduction of functionally active normal cells to carry oxygen, while the recipient's hæmoglobin is fixed by CO, has long been advocated and supported by experimental observations. If it is done after a preliminary venesection it gives good results.

Technique. Quite a number of methods of transfusion are in use. They fall into four main groups.

1. Direct transfusion (arm to arm transfusion).
- 2. Transfusion of unmodified and defibrinated blood.
3. Transfusion of citrated blood.
4. Transfusion of preserved red blood corpuscles.

(1) **Direct transfusion.** In this method, the radial artery of the donor and the basilic vein of the recipient are connected together by means of a thin rubber tube with a silver canula at each end, all the connections being sterilised and filmed by boiling in paraffin. The drawbacks of this technique are:—

(a) It is not possible to know how much blood flows from one to the other. (b) It is difficult to estimate the length of time that should be allowed to let the blood flow. (c) Sometimes, on account of active venospasm of the recipient, the blood from the donor does not flow properly.

(2) **Transfusion of unmodified blood (who's blood).** There are three different methods—Kimpton's, Unger's and Lindemann's. These methods came into being with the idea of obviating the difficulty of ascertaining the amount of blood that is being transfused in the 'arm to arm' method. The main principle on which these methods are based, is that the blood is drawn from the donor into a glass syringe with a stop-cock arrangement, and is then infused into the recipient as quickly as possible.

There is greater risk of massive clotting, for some time must necessarily be spent on the operation and consequently there is greater chance of intravascular thrombosis. Defibrinated blood has been used to get over the difficulty of thrombosis, but the complete defibrination of a specimen of blood is practically unattainable.

(3) **Citrated blood method.** Blood from the donor is drawn into a vessel containing sodium citrate solution (3.8 per cent. sodium citrate

solution is isotonic). As the blood is flowing into the vessel, it is kept constantly agitated to prevent clotting. This citrated blood is then injected into the recipient as quickly as possible though delay up to half an hour is not harmful.

A note of warning has been sounded by some authorities as to the toxicity of the sodium citrate injected. It is said that it gives rise to undesirable reactions and that it reduces the coagulation time of blood which is a distinct disadvantage when transfusion is done as a prophylactic measure before operative measures. Short (1919), however, found no difference in coagulation time after the injection of citrated blood in ordinary dosage (30 oz. of blood in 160 c.cm. of 3.8 per cent. sodium citrate solution).

(4) **Transfusion of preserved red blood cells.** Recent researches have shown that loss of blood after severe hæmorrhage can be replaced just as easily and efficiently by red blood corpuscles suspended in Locke's fluid as by fresh whole blood. The plasma cannot be preserved in citrate dextrose solution without the production of changes which might be toxic to the patient. Rous and Turner have demonstrated that red blood corpuscles preserved in citrated dextrose solution may be stored for several weeks and they still function when injected into an animal of the same species after a hæmorrhage. If however they are kept too long (4 weeks in man), they do no harm, but are rapidly removed from the circulation and the red blood corpuscles and hæmoglobin come down to the original level produced by the hæmorrhage. This method proved to be very useful during the War but it has not been practised in civil surgery.

Transfusion of blood from animal into man. This method has a great supporter in Cruchet. He strongly advocates its use and has adduced a lot of experimental evidence in favour of the method. According to him transfusion of heterologous citrated blood (animal to man) is almost as harmless as transfusion of homologous citrated blood from man to man, if the whole procedure is carried slowly. He maintains that the reactions noted after blood transfusion are due more to rapidity of injection than to hæmolysis or agglutination of the different elements of the blood. These claims have not been universally accepted and this method of heterologous transfusion has not attained any popularity.

Complications of blood transfusion. In many cases transfusion is followed by a minor reaction; soon after the transfusion has been given, the patient shivers and the temperature rises to 100°F. or higher. These small rises of temperature following transfusion are of common occurrence and may be due to one factor or to a combination of factors. The most frequent causes of this reaction are probably minor degrees of incompatibility of red cells and serum. This factor will be dealt with

at length below. Other causes are, a possible incompatibility of the white blood-cells; too rapid, too large, or too cold an injection; changes in the blood of the donor as a result of the presence in it of products of digestion, or as a result of the blood having been kept outside the body for a long time; changes induced by contact with foreign substances or to undue agitation of the blood previous to its administration. The most common complications are:—

To the donor. The risk is insignificant. A donor can without any harm to himself give a pint of blood and can walk about with ease after the operation. In practice it is always better to enjoin rest in bed for a day after removal of the blood. There may be a feeling of exhaustion and emptiness if more blood is withdrawn at one sitting. In America, there are lots of professional donors who allow themselves to be bled every 3 or 4 weeks. It has been proved by eminent workers in America that the same donor may be used repeatedly without ill effects to himself, provided sufficient time is allowed for the regeneration of the blood.

To the recipient. (i) *Hæmolysis.* If the blood of the donor does not match with the blood of the recipient. Alarming symptoms frequently appear when the samples of blood are not compatible, due either to the hæmolysis of the transfused corpuscles or to their agglutination. There may be vomiting, dyspnoea, urticarial rash, quick weak pulse and perhaps convulsions and coma at the time of transfusion. Hæmoglobinuria may appear after transfusion and deaths have been reported. The appearance of these reactions naturally gave such a rude shock to blood transfusion therapy at the time of its inception that it was practically abandoned for a long time. The researches of Moss regarding the different blood groups have brought the method again into general acceptance.

(ii) *Transmission of diseases.* Another risk is the communication of diseases, syphilis has been proved to be conveyed to the recipient, and malaria might also be conveyed.

(iii) Faulty technique may give rise to infection; but blood being definitely bactericidal, the occurrence of this complication is very rare.

(iv) *Anaphylaxis.* A phenomenon similar to anaphylaxis may sometimes occur in patients who have undergone repeated transfusion. This can be controlled by selecting a donor of a group identical with that of the recipient or by using different donors each time. If however the hypersensitive state becomes apparent, the transfusion should be immediately discontinued.

Blood groups. It is rather a strange phenomenon that the blood of different individuals, even of the same family, are not always compatible with each other. Shortly after birth the blood takes up the characters of one of the four groups and these apparently persist unchanged throughout life. The blood of a patient of a particular

group can be given safely to another person of that group but not necessarily to a person belonging to another group.

According to Moss, there are 4 classes of bloods, designated as groups I, II, III, and IV. The relative proportion of these groups (in America) and their suitability as donors, are given in the following table:—

Donor	Percentage frequency	Suitable if patient belongs to
Group I.	5	group I.
Group II.	40	group I. II.
Group III.	10	group I. III.
Group IV.	45	group I. II. III. IV.

The easiest method of determining the blood group of a donor is that of Vincent in which it is necessary to keep in stock sera of persons of group II and group III. This is tested on a glass slide against the blood corpuscles of the donor. A slight agglutination may be easily demonstrated within 5 minutes by the naked eye. If the sera of group II and group III are not available, direct matching tests may be done as follows:—The recipient's blood is drawn and is separated into serum and cells. The donor's blood is then drawn and is separated into serum and cells. The recipient's cells are then tested for agglutination against the donor's serum and the donor's cells are tested against the recipient's serum. If both reactions are negative for agglutination then the persons are of the same group.

According to Lloyd (1926) blood grouping tests are of definite value in the technique of blood transfusion and should always be done where possible. Direct matching tests have got their utility too. Extensive researches during recent years have made it clear that there might be abnormal types (other than the 4 blood groups) and high iso-agglutinin titre in certain donors belonging to group IV (universal donors). So from the point of view of the absolute safety of the patient in the operation of transfusion, direct matching tests must necessarily be done, over and above the routine group testing.

Intravenous sodium bicarbonate. The rationale of using alkalis in cases of acidosis has been much discussed. The hydrogen-ion-concentration of the blood under physiological conditions is always kept constant. It is only under pathological conditions that the alkali reserve of the blood undergoes some change, for various errors in metabolism and deficiency of oxygen result in the production of an excess of fixed acid and this is neutralised at the expense of alkali reserve. This exhaustion of the alkali reserve may be replenished by the administration of alkalis, preferably in the form of bicarbonates which are less toxic. For intravenous medication sodium bicarbonate may be used in a 5 per cent. solution. The usual prophylactic dose being 3 to 5 gm. It must be noted here

that the heat of sterilisation drives off some of the CO_2 and thus converts part of the bicarbonate into carbonate. This being highly corrosive to the subcutaneous tissue, great care should be taken to prevent any escape of the solution into the subcutaneous tissue when giving the injection.

Intravenous calcium. Calcium has been used very commonly by the intravenous route. A brief description of its uses and indications will therefore be useful.

The role of calcium in the body is not very clearly understood. It may be regarded, in one sense, as a very inert substance inasmuch as it is deposited in large amounts in normal tissues with a sluggish metabolism, such as bones, quiescent tuberculous foci, areas of fat necrosis and walls of degenerated arteries. The withdrawal of calcium from the body, on the other hand, ushers in symptoms of tetany. It is evident then that calcium is essential to the system. Howell has shown that the addition of calcium to perfusion fluid induces the isolated mammalian heart to beat more energetically and its complete removal puts a stop to the cardiac systole. Another important property of calcium is its influence on the clotting of the blood.

Uses. The property of calcium to stimulate the heart has been made use of in therapeutics in the treatment of various cardiac conditions. It has been used intravenously in pneumonia and in diphtheria to stimulate the heart enfeebled by the toxins of these infections. Its utility in these conditions is however doubtful. Great caution is required as in certain cases it has been known to give rise to thrombosis and other complications.

Calcium activates the fibrin ferment to induce clotting, and for this property it has been used universally to stop hæmorrhage. Administration of calcium by the intravenous route is considered to be the best, as absorption by the oral route is slow and uncertain especially when the hæmorrhage is severe and from inaccessible sources (*e.g.* gastric and duodenal hæmorrhage). Calcium is also used as a prophylactic measure before operative interference in weak and anæmic individuals in whom there is chance of free bleeding at the time of operation.

Tetany is pre-eminently a calcium deficiency disease and in grave cases of this disease when the patient is troubled with incessant convulsions, intravenous injections of calcium are of great help and may actually save the life of patients.

Injections of calcium are beneficial in tuberculosis of the lungs and particularly in tuberculous hæmoptysis. Administration of calcium combats some of the other manifestations of tuberculosis. The night sweats, the incessant coughing and the diarrhoea of intestinal tuberculosis are definitely checked. The mode of action is not clear, as calcium does not appear to have any marked deleterious effects on the tubercle bacillus.

Dosage. Calcium chloride, being an easily soluble salt, is most commonly given by the intravenous route. Recently, calcium gluconate has also been given intravenously. Colloidal calcium is also given in this way but it is better to avoid it as it is likely to produce embolism.

It is always advisable to use the hypertonic solutions, as these are endowed with a greater degree of hæmostatic action than isotonic solutions. A 10 per cent. solution is very useful and of this 5 c.cm. may be given without untoward effects. Ten c.cm. of a 10 per cent. solution have also been frequently injected but may lead to ventricular fibrillation.

Dangers and reactions. When calcium is injected into a vein, great care must be taken to inject it as slowly as possible. Rapid injection and concentrated solutions produce a sensation of intolerable heat inside the body and the patient is apt to become restless during the operation. Ordinarily this sensation passes off in a minute or so, large doses are known to produce depression, ventricular fibrillation and immediate collapse. The depression of blood pressure which is an accompanying factor might also account for the collapse. Calcium chloride is an irritant fluid and if the solution escapes outside the vein, severe pain and necrosis of the surrounding tissues is likely to be produced.

Intravenous hydrochloric acid. Intravenous injections of 1:1000 to 1:1500 hydrochloric acid have been tried in the treatment of disease. Appreciable leucocytosis is undoubtedly produced by such injections but clinical benefit from such treatment is completely lacking.

2. SPECIFIC AGENTS AGAINST PROTOZOAL ORGANISMS

Intravenous medication of specific remedies against protozoal infections is dealt with in Part III.

3. AGENTS USED AGAINST BACTERIAL ORGANISMS

Intravenous iodine. Intravenous administration of iodine has now a definite place in therapy. The evolution of the idea of injecting iodine into a vein is purely empirical, its external antiseptic action suggesting its use internally. No rational explanation of the nature of the action of iodine given intravenously is available. The idea that the action of iodine in the blood stream is almost identical with its external action cannot hold ground in view of the fact that ordinary therapeutic doses are never capable of attaining a lethal concentration for bacteria in the blood stream. One grain of iodine (contained in about 2 c.cm. of tincture of iodine B. P., the usual therapeutic dose) in 5 litres of the blood cannot have any direct antiseptic action. There must therefore be other factors responsible for the effects which are produced. The view that iodine stimulates the thyroid gland and thereby produces its beneficial results is now generally accepted. Assuming that the thyroid

gland plays a part and the action is an indirect one, small doses of iodine ought to act as well as large doses. It has been shown from case records, however, that larger doses (*i.e.*, 2 c.cm. of tincture of iodine) give decidedly better results than smaller ones. The present position of our knowledge regarding the rationale of the intravenous injection of iodine is thus not quite clear. There is however always a marked leucocytosis after intravenous injections of iodine. This might explain the beneficial results, for increase in leucocytes means an increase in the resistance and fighting powers of the body.

Uses. Injections of iodine have been used in the following conditions :

Septicæmia. Tincture of iodine in distilled water or aqueous solution of iodine has been used in plague septicæmia with gratifying results. It has been given an extensive trial by various workers and the consensus of opinion is that intravenous injections of iodine are perhaps the best remedy against plague. After one to two injections, the general condition of the patient improves, the delirium disappears and the temperature shows a marked tendency to return to normal. In influenzal septicæmia, erysipelas and typhoid fever, it has also been used with good results. As a matter of fact, iodine intravenously has been and is still being used empirically in almost all cases of remittent pyrexia of unknown origin characterised by delirium and rigors, and most cases are said to respond favourably.

Pyæmia. In pyæmic conditions following septic tonsils and sinus trouble, chronic hip diseases, abortion and other puerperal conditions, iodine intravenously is one of the most potent remedies we have at our disposal. Bell (1924) recommended iodine instead of vaccine in places where bacteriological facilities are not available, and he even asserts that iodine will probably replace vaccine therapy in pyæmia.

In lobar pneumonia, post-operative pneumonia and similar lung conditions iodine is of great value. It not only clears up the local condition in the lungs, but also improves the general toxæmia which is so frequently associated with these conditions. The leucocytosis which is set up might account for the beneficial effects which are produced.

Joint troubles like synovitis and arthritis. Iodine has been used in synovitis of the joints with beneficial results.

Chronic ulcers including corneal ulcers. These conditions sometimes respond very well to iodine treatment.

Malaria and kala-azar. Injections of iodine have been tried in both these diseases by Bracho (1923) with indefinite results. Other workers have definitely found them to be useless.

Syphilis. Iodine intravenously has been found to be of no value in syphilis, although potassium iodide is very efficacious in certain stages.

Goitre. Reddi (1927) has recorded a few cases of improvement in goitre by the use of sodium iodide in the China hills.

Dosage. Tincture of iodine diluted in distilled water and aqueous solution of iodine are both used for intravenous medication. The B. P. tincture is more convenient, as it is always available and does not require special preparation. Most people, however, use the aqueous solution with the idea that there is less chance of thrombosis at the site of the injection. Both the preparations, however, are equally effective. One c.cm. of tincture iodine diluted with 2 to 5 c.cm. of distilled water is the dose ordinarily given, the maximum dose being 2.0 c.cm. diluted with 10 c.cm. of distilled water.

The aqueous solution of iodine contains iodine crystals 24 grains, potassium iodide 36 grains, dissolved in one ounce of distilled water. One to 2 c.cm. of this can safely be given (1 c.cm. equals approximately 1 grain of iodine). This solution might be further diluted according to the condition of the patient and the discretion of the physician.

Dangers and reactions. There are no serious risks attendant on these injections. Frequently after an injection febrile reactions associated with rigors set in. These do not require any special treatment excepting rest, hot drinks and warm blankets. Urticaria and iodism have been recorded from time to time but these occur very rarely. Thrombosis of the vein at the site of injection is due to faulty technique and with care can be avoided.

Hexamine (urotropin). Hexamine or hexamethylenetetramine is a compound prepared by the interaction of ammonia and formaldehyde. Hexamine derives its usefulness in therapeutics from its property of easily liberating the latter substance from its combination. This liberation is brought about either by the action of heat or by weak acids. Hexamine is usually given *per os* and is a valuable urinary antiseptic as formaldehyde is easily liberated in the urinary passages. There is also a chance of the formaldehyde being liberated in the stomach by its interaction with the acid of the gastric juice. It is therefore suggested that it should be given by the intravenous route; the blood being alkaline, hexamine will not be broken up in it.

Uses. In septic conditions of the genito-urinary tract, *e.g.*, cystitis and pyelitis, hexamine intravenously is now used universally with very satisfactory results. *B. coli* infections clear up very rapidly. Gonococcal cystitis also responds favourably in most cases. The usual dosage employed is 5 to 10 c.cm. of a 10 per cent. solution. In acute cases, pain, fever and dysuria disappear after one or two injections. In chronic cases more injections are required, the treatment being combined with saline diuretics and local bladder washes.

***B. coli* septicaemia.** Hexamine has been used with satisfactory results in these conditions. *B. coli* septicaemia is the usual outcome of primary infection of the genito-urinary tract and is especially common during the puerperium. It sometimes appears in a very

virulent form and is not amenable to any form of treatment excepting hexamine intravenously. Stronger solutions of hexamine (20 per cent.) have been tried in these conditions on alternate days, without any untoward effects.

Influenza. Intravenous injections of hexamine were extensively used during the influenza epidemic of 1918. One or two injections were enough to control the temperature and the general condition of the patient improved; the naso-pharyngeal catarrh and muscular pain disappeared very quickly. Complications like broncho-pneumonia were unknown in cases treated with hexamine.

Encephalitis lethargica and meningitis. Hexamine has been tried in encephalitis lethargica, especially during the acute stage in doses of 5 c.cm. of a 20 per cent. solution daily for 10 days, with beneficial results. In cerebrospinal meningitis too it has been used extensively.

Mastoiditis and sinusitis. Hexamine has been tried in the treatment of all inflammatory conditions of the mastoid and the sinuses. Such cases usually react well in the early stages but when there is actual formation of pus, surgical intervention is the only rational treatment.

Scabies complicated with suppurative lesions all over the body has been treated with hexamine injections. Although the drug does not act on the causative organisms, it helps to clear up the suppurative condition. The routine suggested is to give 10 per cent. solution in normal saline in doses of 10 c.cm. daily for 3 to 4 consecutive days. The external lesions are washed with plain hot water and a mild sulphur ointment applied.

Acute and chronic nephritis. The rationale of its use in these conditions cannot be explained but diuresis appears to be fairly constantly produced; the irritating effect of formaldehyde probably stimulates the renal epithelium. It is better to withhold hexamine, for it might actually cause further damage to the renal epithelium.

Dangers and reactions. Hexamine injections are attended with no risk if the following points are attended to: (1) the water used must be double-distilled and sterile, (2) the solution should be made in cold water, (3) no acid should be in contact with the solution.

Cases of hæmorrhagic cystitis following intravenous injections of hexamine in doses of 5 to 10 c.cm. of a 40 per cent. solution have been recorded. This might be ascribed to liberation of large quantities of formaldehyde in the bladder irritating the already congested and inflamed mucosa. Weaker solutions, however, seldom cause any trouble.

Colloid metals. Certain metals and metalloids in the form of colloidal solution are used in therapeutics. The metal exists in these solutions in a state of very fine subdivision, and the colloidal solution of a metal resembles more nearly a suspension of metallic dust, than it does a solution. The particles in this condition are one to one hundred micromillimetres in diameter and therefore readily pass through the capillaries.

and do not produce emboli. They consist of aggregates of a large number of molecules and very few ions of the metal are present. The whole of the metal, in a colloidal solution is therefore in an inert state and the free ions which are liberated are so few that they do not produce irritation, but are sufficient to produce an oligodynamic action which inhibits the growth of bacteria. Moreover, the metal in this state may pass quite readily into ionic conditions, *e.g.*, by the action of tissue fluids, bacteria, etc., and may then exert the ordinary action of metal. Bayliss has criticised the claims that have been put forward in favour of the pharmacological activity of the colloid metals. He points out that the 'electrical charges' and the 'surfaces' in dilute solutions of colloid metals are insignificant in comparison with those that already exist in the protein systems of the blood and tissues; and that many of the effects attributed to the metals are due to the protective colloid and others to the acidity of the solutions.

Most of the electrically or chemically prepared colloids are unstable. For clinical use, they are 'stabilized' by addition of organic colloids, *e.g.*, gelatin, albumen, etc.

Colloidal metals are commonly used for the treatment of infective conditions, *e.g.*, puerperal septicæmia, pneumonia, pleurisy, peritonitis, influenza, typhoid, tuberculosis, and other febrile conditions. Repeated intravenous injections may often produce marked irritation of the lymphoblastic tissue of the spleen, lymph glands and bone marrow. Moreover, colloid solutions, deteriorate on keeping and gradually pass into the ionised form, which may produce the ordinary systemic effects of the metal. They may also rapidly pass into insoluble forms and may then produce embolism. These effects should always be taken into consideration while using a colloid metal.

The following are the preparations commonly used.

Colloidal copper solution. It is generally used in cases of inoperable malignant growths, and it is believed that on the surface of the metallic particles, it supplies oxygen necessary to prevent abnormal cell growths. Strength of the solution used is 1: 2000 and the dose 1/2 to 1 c.cm. intravenously. The solution is to be made isotonic at the time of use (sodium chloride should not be used for the purpose, since electrolysis may cause precipitation).

Collosol iodine. It is used as a substitute for iodides in cases of syphilis, rheumatic affections, tuberculosis, bronchial and nasal catarrh. Ten to 200 c.cm. may be used intravenously, and in cases of pyæmia and to produce softening of fibrous tissue as much as 300 c.cm. has been given intravenously.

Colloidal mercury solution. This is used in syphilitic affections in doses of 5 c.cm. of 1 in 2000 solution (0.0025 gm. of metals). The solution may be isotonised at the time of injection by 1 c.cm. of 5.5 per cent. sodium chloride solution.

Colloid silver solution. It has been particularly used as an internal antiseptic in puerperal septicaemia and other infections. Phagocytosis is perhaps somewhat increased for some bacteria but not all. The dose is 5 c.cm. of 1: 2000 solution intravenously.

Colloidal gold solution. Orargol is a preparation of colloid gold (0.01 per cent.) and silver (0.09 per cent.). It is used in doses of 5 c.cm. intravenously or intramuscularly to abort attacks of pneumonia, influenza or erysipelas.

Colloid bismuth has been largely used in the treatment of syphilis and is described in a separate chapter.

Collosol sulphur. It is used in skin affections and wherever sulphur is indicated through excessive elimination, solution of 1: 1000 in doses of 1 to 2 c.cm. is used, which at the time of injection is made isotonic with 0.4 c.cm. of 5.5 per cent. saline.

4. Intravenous administration of immunity-producing agents, *e.g.*, sera and vaccines, is dealt with in Part V.

5. INTRAVENOUS ANAESTHETICS

Magnesium sulphate. A soluble salt of magnesium injected intravenously into a rabbit produces a complete loss of excitability in all parts of the nervous system. Not only is the central nervous system paralysed, but the drug also produces a curariform action and paralysis of the motor nerve endings. In concentrations of 0.1 per cent., magnesium in the blood stream will produce this action and the action is immediately abolished by injecting an equal amount of calcium. The pharmacological action of magnesium differs fundamentally from other hypnotics. Most hypnotics act first upon the higher centres of the brain and produce a descending paralysis of the central nervous system but magnesium acts indifferently upon all the parts of the central nervous system. The action of magnesium is a reversible one and if an animal is kept alive by artificial respiration it recovers after a time from magnesium anaesthesia.

Therapeutic uses. 1. Intravenous injections of magnesium sulphate have been recommended as a treatment preliminary to ether anaesthesia, the drug acting very much like morphia before chloroform, in reducing the minimal concentration necessary to induce anaesthesia. Cases of excessive oral administration of magnesium sulphate are known to have caused a comatose condition in man, but the usual purgative doses do not produce this effect as magnesium is very slowly absorbed from the gut and is rapidly excreted by the kidneys.

2. To relieve labour pains, intravenous injections of magnesium sulphate have been tried, instead of morphia, in morphia-scopolamine or twilight sleep. Here magnesium acts as a synergist to scopolamine and potentiates the action of the latter drug. It is, however, seldom used for this purpose.

3. **Tetanus.** In this condition intravenous injections of magnesium sulphate have been employed 10-15 c.cm. of a 3 per cent. solution being injected without any danger to the patient. Stronger solutions produce sudden coma and death from respiratory paralysis. A 20 per cent. solution of magnesium sulphate may also be used, alternating with carbolic acid, to control the tetanic convulsions.

4. **Eclampsia.** Reports on the use of magnesium sulphate in the treatment of eclampsia are very encouraging. It is well worth a more extensive trial by obstetricians. Chloroform and other hypnotics are, however, better than magnesium sulphate as an anti-spasmodic.

Evipan-sodium. Evipan sodium is the sodium salt of N-methyl-c-cyclo-hexenyl-methyl-barbituric acid which dissolves freely in water. It is put up in dry ampoules containing the drug in powdered form, which is dissolved in sterile distilled water to form a 10 per cent. solution. It is used intravenously either as a basal narcotic or as a general anaesthetic for minor or major operations. The dosage depends upon the individual consideration of the surgeon. The body weight is too uncertain a factor to serve as a guide. All that one has to do is to watch carefully the dosage which is producing sleep and according to the nature of the operation the dose is increased to get the desired depth of anaesthesia. In small operations 2-3 c.cm. will be sufficient; for more prolonged operations a dose of 8-11 c.cm. produces a smooth and perfect anaesthesia lasting from 20 to 35 minutes and sometimes even longer. There is usually no untoward after-effects and in no case is anything found to show that evipan has any deleterious effect on any organ. Evipan is not suitable for feeble or toxæmic patients or those with cardiac and respiratory failure.

6. AGENTS THAT CAUSE SCLEROSIS OF THE VEINS

The application of injection therapy to such conditions as hæmorrhoids, varicose veins and allied lesions has recently come to the forefront. These conditions were previously treated by surgical methods which were not always successful. In surgical treatment, anaesthesia with all its dangers and complications is an important factor. Added to this is the prolonged rest in bed and consequent loss of time and money. Injection treatment is free from all these disadvantages and probably has thus given comparatively better results. The latter method of treatment has therefore been largely adopted within recent years.

A. **Hæmorrhoids.** Hæmorrhoids are quite common in people residing in the tropics. Palliative and operative treatment used to be carried out in almost all the cases. Injection treatment has now placed in our hands a safe and efficient method of treatment. The type of patient who will react best is the one whose main symptoms

are hæmorrhage with or without an associated mild degree of prolapse. Phenol 5 per cent. in almond oil or olive oil is the most satisfactory substance to inject. The aim of the method is to glue the rectal mucosa to the muscular wall and hence the injection is made high up into the rectal sub-mucosa and not into the piles itself. Quinine and urethane have been tried but these tend to produce sloughs and a brittle rectal mucosa. The advantages claimed for this method are :—

1. The method is less painful and less dangerous.
2. It is ambulatory.
3. It is less expensive in time as well as in money.
4. The incidence of recurrence is less than after operative interference.

5. The danger of the formation of a stricture, one of the common complications of radical operation for piles, is entirely eliminated.

Technique. The solution is readily prepared by melting phenol crystals over a water-bath and adding an equal volume of warm almond or olive oil. This makes a 50 per cent. solution and it may be preserved as a stock solution. The solution is sterile by virtue of its phenol content. The solution to be used is diluted before use by adding nine parts of warm almond oil.

The patient is placed in the left lateral position. Emptying the rectum is the only pre-operative preparation necessary. The speculum is inserted and a point well above the pile-bearing area is chosen. One to 2 c.c. of phenol solution is injected into the submucosa but not into a vein. Two areas may be treated every 5 to 7 days and at each subsequent treatment an area a little lower in the rectum is chosen. After 5 or 6 treatments the patient is usually cured and the pile becomes as hard as a piece of parchment.

B. Varicose veins. The treatment of varicose veins has been revolutionized by the introduction of intravenous sclerosing agents and operative interference is now practically dead. This treatment can be practised on any patients whatever their age, and it is practically universally applicable in all cases. Where the varicosity is due to some secondary complications such as a growth in the pelvis, advanced systemic disorders or deep-seated bacterial phlebitis, it is always safe to avoid giving injections. During pregnancy, due to the pressure of the enlarged uterus, varicose veins may appear in the legs. It is always better to treat these varicose veins by sclerosing agents, though some authorities have treated them by injections during the early period.

Sclerosing agents. Unlike the treatment of piles, there is no agreement as to the best solution to be used in the treatment of varicose veins. Different observers have recorded successful results with different solutions. The sclerosing agents most commonly employed today will be discussed below.

Quinine and urethane mixture. The mixture commonly used consists of a 13 per cent. quinine and 6.5 per cent. urethane solution, and 2 to 3 c.cm. is usually injected. The quinine is the important constituent and brings about endotheliolysis. The urethane is added for its anaesthetic effects so that the actual pain is much less. The advantage of this preparation is that it nearly always produces a thrombosis and consequently not more than 2 or 3 injections are required in the majority of cases.

The reaction induced by the quinine is a severe one, and sometimes the whole saphenous vein becomes filled with clot, following one injection only. The vein usually remains inflamed and painful for six weeks or so. Faulty technique with this solution is always attended with severe results. If the quinine escapes through the puncture and if a thin-walled vein is chosen for injection, the results may be a sloughing ulcer taking a pretty long time to heal up. General toxic manifestations are sometimes noticed.

Contraindications. General systemic diseases such as cardiac and renal diseases are not contraindications. Acute phlebitis, intermittent claudication, deep thrombosis and phlegmasia alba dolens, etc., should be avoided. During pregnancy the treatment may be carried on according to requirements.

Hydrocele and Varicocele. Injection of sodium morrhuate has also been tried in hydroceles and varicoceles. Although there is a growing opinion that injection treatment is a good method, the idea has not yet gained popularity.

7. AGENTS INJECTED INTRAVENOUSLY FOR DIAGNOSIS

Recently, a number of drugs have been introduced in medicine which are used for diagnostic purposes. These find their most important application in radiography. Sodium tetraiodophenolphthalein has been used in gall bladder radiography and uroselectan B in pyelography.

Uroselectan B is a pyridine derivative with 51.5 per cent. of iodine in close organic combination.

According to clinical trials made by Professor A. Von Litchtenberg in the Urological Department of St. Hedwig's Hospital, Berlin, the intravenous injection of the contents of one 20 c.c. ampoule is sufficient to give pyelograms which provide all the detail necessary for diagnosis.

Children must naturally be given smaller doses in view of the reduced capacity of their circulatory system.

Technique of injection. Uroselectan B is supplied in 20 c.cm. ampoules sterilised ready for use. Each ampoule contains 15 grams

of the substance dissolved in a 10 per cent. solution of invert sugar (a mixture of equal parts of dextrose and laevulose). The ampoules are warmed to body temperature in a water bath. The contents are then injected as slowly as possible into the cubital vein with an ordinary 20 c.cm. syringe.

As in the injection of any other hypertonic solutions care must be taken that the needle lies centrally in the lumen of the vein and that the injected fluid becomes diluted as far as possible by the blood stream. In this way damage to the intima will be avoided. The use of a fine needle is an advantage, provided that it is borne in mind, that the intima is more easily injured with such a needle, and particular caution is exercised to avoid this.

When it is correctly administered, the injection of Uroselectan B is very well tolerated; there need be no fear of the occurrence of venous thrombosis.

Pyelography. When only anatomical information is desired, it is as a rule sufficient to take a single pyelogram 20 to 30 minutes after the injection. In cases of calculus, displacements and similar anomalies, this method will almost invariably give the information required. If, however, a more exhaustive urological investigation is necessary, in order to demonstrate the functional efficiency and dynamics of the urinary tract, a series of exposures must be made.

The first exposure is made 10 minutes, the second 30 minutes and the third 50 minutes after injection. It has been observed, however, that in many cases when renal function is normal, the best films are obtained 2 to 5 minutes after injection. Before the second and third exposure the bladder should be emptied so that the shadows of the pelvic portions of the ureters are not obscured. In patients with considerable disturbance of renal function satisfactory pyelograms first appear not later, and may not become sufficiently clear for the purposes of demonstration, for 6 to 24 hours after the injection. If the kidney function is completely suspended, permanently or temporarily, no uroselectan B will be excreted and it will be impossible to obtain a pyelogram.

In general, care should be exercised in employing uroselectan B in patients with severely impaired liver function or with acute or chronic uraemia, all the more, as frequently no pyelogram of any value for diagnosis will be obtained. Further, it should be employed with caution in cases where the urinary disease is accompanied by severe general disease.

Cholecystography. Certain substances, when injected subcutaneously, are excreted exclusively through the biliary passage. Some of these used for testing the global capacity of the liver are opaque to x-rays

and these are employed for obtaining cholecystograms. Various substances are used for this purpose and of these the sodium salts of tetra-iodo-phenolphthalein is the most opaque to x-rays so that a smaller dose is required. Formerly, the intravenous route was adopted for this purpose, usually about 3 gm. for an adult or 0.048 gm. per kilo. body weight. Nausea and vomiting accompanied by a marked fall in blood pressure were often observed. In view of the frequency with which these toxic manifestations have followed the intravenous injection, this method of administration has been given up. Oral administration is the method of choice now-a-days and there is very little, if any, risk of provoking toxic reactions when any of the salts, either bromo or iodo, are given by mouth.

Cerebral angiography. A study of the radiological appearances of the cerebral blood vessels after injection of opaque solution into the carotid artery, is an important aid in the diagnosis of some intra-cranial growths. In view of the fact that it reveals important new anatomical and physiological findings, mention of this is made here. 'Thorotrast', which is claimed to be a stabilized thorium dioxide solution containing 25 per cent. by volume of thorium dioxide (ThO_2), along with a preservative (0.15 per cent. of methyl-p-hydroxy benzoate), is generally used for obtaining a radiogram of the intracranial blood vessels. Ten to 16 c. cm. of thorotrast is injected into the lower part of the common carotid artery and a series of radiograms at intervals of one second is taken. By this means it has been possible to display the cerebral veins and sinuses as well as the arteries. This procedure is quite safe and not attended with any inconvenience to the patient. It is, however, doubtful whether cerebral angiography has got any special advantage over ventriculography as the main accessory method available for the diagnosis of intracranial tumours.

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CHAPTER IV

ACIDOSIS AND ALKALOSIS

These terms were first introduced at a period when there was no exact knowledge regarding the reaction of blood. It was thought at the time that the reaction of blood altered freely, whereas we now know that there is an elaborate mechanism at work for maintaining the reaction of blood at a constant level and that only small changes occur during life. The term acidosis has been applied to a condition in which there is an increase in the amount of CO_2 in the blood or to an increase in the fixed acid of the blood; but it has given rise to so much confusion that it is better to abandon the term altogether and to speak of a decrease in the alkali reserve of the blood. Sellard defined acidosis "as a diminution in the reserve supply of the fixed bases in the blood and other tissues of the body, the physico-chemical reaction of the blood remaining unchanged except in very extreme conditions. The definition should not be limited to the carbonates alone, but should include other fixed bases of the body; likewise the changes should not be limited to the blood, but should include the other tissues as well." Acidosis, therefore, really means some change in the blood which, if uncompensated, would alter the reaction of blood towards the acid side and alkalosis means that which would alter it towards the alkaline side.

It is very easy to change the reaction of a fluid like water, which only contains H and OH ions. Blood however is a very complex substance, and the hydrogen-ion concentration of blood is perhaps one of the most constant things in nature. In spite of the fact that a number of factors, such as production of acid from metabolic processes and muscular exercise or draining of acid from blood during gastric secretion, etc., are constantly tending to alter the reaction of the blood, the regulating mechanism is wonderfully efficient in keeping the same constant. This is only possible because blood contains a number of sub-

tances, such as acid and alkaline phosphates and sodium bicarbonate, which together with the hæmoglobin and protein act as a powerful 'buffer' and prevent the reaction of the blood being easily changed. Further, other regulating mechanisms are at work, since urea can split up into carbon dioxide and ammonia, the former can be excreted by the lungs, while the latter can be used to neutralise any acid. The kidneys can excrete acid or alkali salts which may be in excess, and thus help to maintain the acid base equilibrium constant. Henderson considers carbonates of the blood as the first line of defence against acidosis. A second line of defence is the capacity of the kidneys to excrete an acid urine from a neutral blood; they remove the acid phosphates and save the base. A third line of defence is furnished by the proteins. Proteins can combine with appreciable amounts of either acids or alkalis without undergoing any marked change in reaction. Another line of defence is ammonia, which the body produces, whenever there is a demand, at the expenses of urea.

Briefly the various factors that are constantly at work to maintain the acid base equilibrium can be grouped under the following heads;—

1. The intrinsic property of blood.
2. The renal factor.
3. The metabolic factor.
4. The respiration.

1. The blood normally contains some buffer salts which give it the property of maintaining its reaction always constant. The phosphates in forms of Na_2HPO_4 or NaH_2PO_4 play a very important role in the buffering action. The addition of acids or alkalis, results in the formation of compounds which do not give free H or OH ions in solution and consequently the reaction of the blood is not influenced. Sodium bicarbonate also plays a similar part, weak H_2CO_3 is liberated when it is acted on by an acid and a neutral salt is formed. The H_2CO_3 is quickly excreted in form of H_2O and CO_2 . The buffer substances present in the blood constitute the true alkali reserve and it is the alkali reserve that undergoes the chief changes in

disease. It is usual to estimate alkali reserve in the form of sodium bicarbonate and a measure of it would indicate the extent of the acid condition, a low figure pointing to a serious state. Depletion in the alkali reserve precedes a rise in the hydrogen-ion concentration and hence, is a valuable indication for treatment.

2. The renal factor. If the carbonates in blood were the only method of defence of the body the organism would die from acidosis as soon as the bicarbonate was depleted by the excretion of neutral salt through the kidney; every molecule of acid would rob the body of a molecule of bicarbonate. The second mechanism comes into play and that is the remarkable power of the kidney to secrete urine of widely varying reaction from the blood of a constant hydrogen-ion concentration. The kidneys thus remove acid phosphates and some base with each molecule of acid phosphate that they excrete. Thus although alkali is eliminated in the urine, it is much less than would be the case without this specialised kidney activity. The method by which the sodium bicarbonate reserve of the body is renewed may be expressed by the following:—

$\text{Na}_2\text{HPO}_4 + \text{HCl} = \text{NaCl} + \text{NaH}_2\text{PO}_4$ the hydrochloric acid is neutralised and the sodium chloride and acid sodium phosphate are excreted by the kidneys.



the acid sodium phosphate is excreted. Therefore one of the renal functions would be to keep the ratio $\frac{\text{NaH}_2\text{PO}_4}{\text{Na}_2\text{HPO}_4}$ constant by excreting one or the other as the case may be. In this manner the kidneys will excrete the hydrogen ion.

3. The metabolic factor. The metabolism of protein, carbohydrate and fat causes the appearance of non-volatile acids as intermediate products of metabolism, which under normal condition are oxidised to form CO_2 and H_2O . The protein nitrogen is first deaminated in the liver, and an oxyacid and ammonia are set free. Normally the greater part of ammonia combines with CO_2 and water, forming ammonium carbonate, which, in turn, is converted into urea and eliminated as such.

Any excess of non-volatile anions over kations is adjusted by the kidney, which usually secretes urine of high acid reaction.

4. **Respiration.** The physiology of the respiratory centre is most interesting, for when the amount of acid increases in the body, there is a quick stimulation of these centres, with the result that more CO_2 is thrown out and the fixed acid of the blood is prevented from assuming large proportions. The respiratory centre is extraordinarily sensitive to the slightest alteration in the reaction of blood towards the acid side, so that an increased production of carbon dioxide in the tissues and the resultant slight excess in the blood is answered by an increased ventilation of the lungs. It appears that the body uses this weak volatile acid for fine adjustment of the blood reaction, a condition of acidosis being accompanied by washing out of acid in form of CO_2 , while an alkalosis is compensated by the retention of this substance.

In clinical practice the danger in disease lies in the exhaustion of the alkaline reserve in the blood and this may be the result of (1) increase in the fixed acids present in the blood after violent muscular exercise or in diabetes and renal diseases, (2) reduction in the fixed acid, (3) interference in the excretion of carbon dioxide, (4) excessive excretion of carbon dioxide in certain types of pneumonia, (5) non-gaseous acidosis in disease.

The measure of the degree of acidosis consists in the estimation of:

1. Lowered carbon dioxide combining-power of the blood.
2. Lowered alveolar carbon dioxide tension.
3. Degree of affinity of hæmoglobin for oxygen.
4. Reduced alkalinity of the blood.
5. Increased hydrogen-ion concentration of the blood.
6. Increased intensity of urinary acidity.
7. Retention of alkali in the body.

Non-gaseous acidosis. The metabolism of proteins, carbohydrates and fats, produces non-volatile acids, which normally are oxidised into CO_2 and H_2O , whilst proteins are excreted as urea. The kidneys excrete urine with strong acid reaction and in this way eliminate the excess of non-volatile anions. This state of affairs may be disturbed in disease, resulting in reduction of alkaline reserve and reaction of the

blood shifting towards acidity. This occurs (1) when there is failure of respiration and circulation and the supply of oxygen to the tissues is deficient. (2) In diabetes where the cell metabolism for carbohydrates and fats becomes abnormal. In injuries of the liver also acidosis is produced. (3) In kidney disease fixed acids accumulate in the body.

Administration of large doses of calcium chloride and ammonium chloride produces a reduction of alkaline reserve in the blood. The ammonium chloride is changed into urea by the liver liberating HCl and H_2O . The calcium ion of calcium chloride forms calcium carbonate in the gut which remains unabsorbed and the excess of chloride is absorbed which produces acidosis. The onset of acidosis is accompanied by diuresis.

A large amount of partially oxidised products of metabolism are produced after a short period of violent physical exercise. After half a minute of violent exercise a subject can incur an oxygen debt of 16 litres and the oxidation of the products of partial catabolism after a debt of this magnitude take more than an hour to complete. Such oxygen debt corresponds to about 70 gm. of lactic acid, a quantity that would produce an average concentration of 0.12 per cent. lactic acid in the body. Not more than 0.1 to 0.2 per cent. lactic acid appears in the blood in such cases and probably most of the lactic acid is neutralised temporarily by the muscle protein. In uncompensated cardiac disease the most striking feature is the inability to oxidise any excess of lactic acid produced as a result of exercise.

The chief symptom of acidosis is dyspnoea and in addition to this there are usually symptoms due to the particular defect that caused acidosis.

Acidosis in diabetes. The defective oxidation of the fats in diabetes results in the formation of β -hydroxybutyric acid, aceto-acetic acid and acetone. The interaction of these organic acids with the sodium bicarbonate of the blood, results in the taking up of sodium by the acids and the setting free of CO_2 , thus robbing the body of its alkaline reserve. Allen states that fasting checks the acetone formation and that alkali holds no more than an adjuvant position. There is little need for the use of sodium bicarbonate in the treatment of diabetic acidosis at the present time, as insulin is almost a specific.

Acidosis in nephritis. The kidneys secrete daily an amount of acid corresponding to 20–50 c.cm. of normal acid. This quantity is insignificant when compared to the quantity of acid

excreted by the lungs as CO_2 , for the lungs excrete about 1500 gm. of CO_2 daily. The acid secreted by the kidneys however is non-volatile which cannot be excreted by the lungs, and if this acid was retained in the body, it would rapidly exhaust the alkaline reserve of the blood. The urine contains phosphates which act as buffers and prevent the acid excreted, producing a degree of acidity which would be irritant to the bladder. The reaction of urine varies from pH 5 to pH 8. Many cases of chronic renal diseases show a more or less pronounced acidosis with marked nitrogen retention. Cases of acute nephritis may occasionally show a severe acidosis. Favourable results are obtained in these cases by the administration of alkali.

Acidosis in children. Acidosis has been found in many cases of severe diarrhoea in children. Those, not attended with ileocolitis, show only a moderate increase in acetone bodies and a deficient excretion of acid phosphate by the kidneys, while with ileocolitis the amount of acetone bodies is very large. The administration of sodium bicarbonate will in most cases bring about a cessation of symptoms of hyperpnoea but a cure can hardly be effected by this treatment.

Acidosis as a result of anæsthesia. The administration of anæsthesia results in a lowering of the CO_2 combining-power of the blood and consequently there is a decrease in the alkali reserve. The initial acidosis of anæsthesia is an uncompensated one, since there is an immediate fall in the pH which precedes the fall in total CO_2 . Hence there is a grave risk run when cases of severe diabetes or nephritis with low figures for the CO_2 are operated on under general anæsthesia. A preliminary administration of sodium bicarbonate increases the alkali reserve and it also leads to higher values for this factor at the conclusion of the anæsthetic.

A condition of 'acidosis' or diminished alkali reserve in the body has been known to occur in different diseases. The diseases in the tropics in which this condition has been recognised are cholera, kala-azar, blackwater fever, malaria, yellow fever, trypanosomiasis and heat stroke.

Reaction of blood in kala-azar. There is very little change in the pH of the blood in this disease, the change being slightly towards the alkaline side. More accurately speaking, it may be stated that in kala-azar the hydrogen-ion concentration of the blood is usually about normal, but the buffer action is reduced.

Acidosis in malaria. As far back as 1895 Steindler and Limbeck reported a diminution in the alkalinity of the blood in cases of malaria. It has now been definitely found out by Sellard's 'bicarbonate tolerance test' that the reaction of blood in malaria points to a moderate degree of acidosis. No marked relationship, however, can be made out between the amount of acidosis present and the intensity of the signs and symptoms.

Acidosis in cholera. The most constant feature in cholera is a great reduction in the alkalinity of blood. From a normal of about $\frac{N}{25}$, it falls to as low as $\frac{N}{60}$ to $\frac{N}{80}$, and in fatal cases even lower. There is also a retention of phosphates in the blood. Our knowledge of this characteristic feature has greatly reduced the mortality rate from this complication. The acidosis, if it has not been allowed to proceed to a fatal degree, can be combated by use of sodium bicarbonate solution for intravenous injection.

Alkalosis. Reduction in the fixed acids can be produced by persistent vomiting, which causes loss of HCl. The alkaline reserve is increased and there is a tendency to alkalosis. A similar condition can be produced by giving large doses of sodium bicarbonate which increases the carbonate content of the blood.

Hyper-ventilation of the lungs causes the washing out of CO_2 from the blood, and a consequent shifting of the reaction of the blood towards alkaline side. Inhalation of irritant gases also produces this condition and it also occurs during hyper-ventilation produced in the initial stages of ether anaesthesia. Alkalosis also occurs in hysterical hyperpnoea.

The symptoms of alkalosis are headache, nausea and vomiting, dizziness and weakness. In severe cases of tetany,

semicoma and convulsions may occur. Tetany is probably produced owing to the fact that increased alkalinity reduces the dissociation of calcium salts and therefore reduces the concentration of ionic calcium present in the blood. It should be realised that alkalosis is a serious condition and the physician should bear in mind when prescribing large and frequent doses of alkalis.

Treatment of acidosis and alkalosis. The treatment of acidosis must be directed chiefly to the care of the derangement of functions that caused the condition, but the actual symptoms can be relieved by intravenous injection of sodium bicarbonate.

The simplest treatment for alkalosis is the inhalation of CO_2 . The calcium content of the blood can be raised by the administration of para-thyroid extract or by the administration of calcium salts by mouth or intravenously.

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CHAPTER V

CHEMOTHERAPY

Historical and General. The search for a specific remedy to cure a specific disease or diseases is as old as the art of medicine. From very ancient times physicians and healers have worked to attain this ideal, and various remedies have been suggested and tried in the treatment of various diseases. In former days chance was the only foundation of their investigation, and empiricism dominated the therapeutic investigation in the treatment of disease. In fact, empiricism still dominates the scientific search for specific remedies and it has not been altogether unsuccessful. There are the examples of cinchona for malaria, salicylates for rheumatic conditions, ipecacuanha for amœbic dysentery, all of which were used empirically centuries ago. The number of specific remedies is unfortunately very small. The modern scientific line of investigation of specifics for diseases is known as 'chemotherapy.'

Before entering into any details it will be convenient to see what the meaning of the word chemotherapy in the modern sense of the term implies. It has been observed before that the use of certain drugs in specific diseases is as old as the art of medicine. The work of scientists like Pasteur, Koch, Lister and others advanced our knowledge of diseases to a considerable extent and the discovery of microbes as a causative agent for infectious diseases, with the almost simultaneous observations about the action of chemicals on these microbes, indicated that the long-maintained theory of finding specific drugs for specific diseases was possibly about to materialize. It was soon discovered that this idea of treating diseases does not hold good in practical therapeutics. Although certain chemicals such as phenol, and mercuric chloride, exerted a very powerful action on bacteria, their action on the body cells was equally marked and the chemicals highly toxic to bacteria were also toxic to the body cells. Their employment in practical therapeutics is, therefore, often not possible.

The discovery of diphtheria antitoxin and its successful use as a curative and prophylactic measure against diphtheria, stimulated the idea of finding antibodies for all bacterial diseases through natural agencies, but it was soon realised that this theory does not hold good.

for the body does not develop immunity in the case of all diseases as it does in the case of diphtheria. It was then thought that rapid advance in synthetic chemistry might give that power into the hands of man which is absent in nature, that it might be possible to evolve certain synthetic products which would be very toxic to the parasites and least harmful to the body cells.

At about the same time as this idea was taking firm root in the minds of scientists, Laveran and Mensil (1902) attempted to cure experimental trypanosomiasis in small laboratory animals with various chemical reagents. Arsenious acid was at that time used in the treatment of animals naturally infected with trypanosomes, and these workers tried this drug as well as many other chemicals for treating this disease. They met with results which did not materially advance the treatment of trypanosomiasis, but their method of investigation was readily accepted for studying the parasitocidal action of a particular drug in relation to its toxicity. Simultaneously Ehrlich was engaged in the study of dye stuffs and their effects upon the cells, and the experimental production of trypanosomiasis in laboratory animals gave an impetus to his studies. This work led to the discovery of the curative action of 'trypan red' in mice experimentally infected with *T. equinum*. After this followed trypan blue, afriol violet and several other synthetic coal derivatives.

Immediately following this work, Thomas (1905) found that atoxyl in combination with trypan red exerted a curative effect in laboratory animals artificially infected with different species of trypanosomes. Ehrlich had tried the effect of atoxyl on trypanosomes *in vitro* before this, but as the trypanocidal activity of this compound was not found to be marked, an attempt to try atoxyl *in vivo* was not then made. Thomas' work attracted Ehrlich's attention and he, in collaboration with Bertheim, after a careful study of the chemical structure of atoxyl considered the possibility of obtaining a large number of chemical substances from this compound which were lower in toxicity but higher in trypanocidal activity. This work eventually led to the synthesis of salvarsan and definitely established the modern science of chemotherapy as a branch of pharmacology.

Shortly after the discovery of atoxyl as a trypanocidal agent, experiments were conducted with spirochaetal infections. It was shown that certain compounds of arsenic, having no spirochaeticidal action *in vitro*, have marked curative properties in spirochaetal infections *in vivo* especially those of relapsing fever in mice and spirillosis of chickens.

Definition and scope of chemotherapy. Although very limited in its original sense, the word has a most extensive application as it now includes both the treatment and prevention of disease by chemical agents which inhibit or destroy the para-

sites without producing any marked effect upon the body cells. Before entering into a discussion about the definition of the word 'chemotherapy' it is essential to understand some of the terms used by Ehrlich, the father of modern chemotherapy, and to consider some of the salient features of the principles of chemotherapy which have a direct bearing on the experiments conducted.

As has been stated before, the discovery of germicidal properties of certain chemicals at one time led investigators to imagine that those chemicals which exerted a marked toxic effect on the specific organisms can be used in the treatment of the disease. It was soon realised that this is true to some extent in local lesions only, and the application of the theory in the treatment of systemic infection is dangerous. Cholera vibrios are readily killed by perchloride of mercury but it is impossible to cure a cholera patient by this drug, for the dose which is necessary to destroy the vibrios in the gut is distinctly toxic to the host.

In considering the principles of chemotherapy therefore two main points will have to be taken into consideration. In the first place, the action of the chemical agent on the parasite should be considered. Some substances have a special affinity for a special kind of parasite and this Ehrlich designated as *parasitotropy* or *parasitotropism*. The special and selective affinity for the chemical agent may be confined to one species of parasite only—*monotropism*, or to several species—*polytropism*. It is not, however, essential that the parasitotropism should be synonymous with the parasitocidal activity of a chemical agent. Atoxyl, as we have already observed, is not strictly parasitocidal *in vitro* but still it exerts a powerful action on the growth and activity of trypanosomes *in vivo*.

The second point which should be considered is the special affinity of chemical agents for the body cells. This Ehrlich termed as '*organotropy*' or '*organotropism*' and modern chemotherapy aims at finding substances which are highly parasitotropic, while possessing the least affinity towards the body cells, i.e., very low organotropism. Diphtheria antitoxin is ideally suited to serve as an example of what a chemotherapeutic

remedy should aim to be. It has a marked action on the *C. diphtheriæ* while it exerts little or no action on the body cells. It is, however, difficult to find chemical substances which will have a potent action on the parasites and at the same time have little or no action on the body cells.

Chemotherapy only requires the proportion of parasitotropism and organotropism to be present to such an extent as to allow the chemical agent to be useful in practical therapeutics. The organotropic effect may not be entirely absent, but it should not make the substance toxic and dangerous. To express the relation between organotropism and parasitotropism, Ehrlich coined the phrase '*chemotherapeutic index*.' It is the ratio between the maximum tolerated dose per kilo. of body weight and the minimum dose per kilo. of body weight required to destroy the parasites in the body. The higher is this ratio the greater is the applicability of the compound in the treatment of disease. Kolmer illustrates this ratio by a concrete example: Arsphenamine by intravenous injection is generally borne by white rats in doses of 0.120 gm. per kilogram of body weight for an indefinite period; 0.140 may kill it in a few days. The former is therefore the M. T. D. (maximum tolerated dose). When administered to rats infected with *T. equiperdum*, the smallest dose per kilo. capable of completely eradicating the infection may be 0.004 gm., M. E. D. (minimum effective or curative dose). The results are expressed as follows:—

$$\text{Chemotherapeutic index} = \frac{\text{Maximal tolerated dose per kg. } 0.120}{\text{Minimal curative dose per kg. } 0.004} = 30$$

This chemotherapeutic index, however, depends upon a number of factors, e.g., the animal experimented upon, the strain of infective organism used, and therefore its value is not constant.

The nature of the phenomenon of organotropism and parasitotropism is still undetermined. The selective affinity of drugs for certain cells only is well known in pharmacology. It is known that strychnine has a special affinity for nerve cells, especially the anterior horn cells of the spinal cord and the narcotics have a special affinity for the fat-like substances. Why these substances have special affinity for a particular kind of cells is still not clear. The nature of parasitotropism and organotropism is suggested to be the same as the phenomenon of special affinity of strychnine for nerve cells and may be purely chemical.

From the discussion given above it will be seen that the requirements of a modern chemotherapeutic remedy are a chemical agent which is highly parasitotropic, least organotropic and which will act in such a way as to eradicate the causative organism from the body of the host without damaging the tissues to any appreciable extent.

Various definitions of chemotherapy are given from time to time and Kolmer gives one which is used in the widest sense of the term and which includes both the prevention and treatment of a bacterial or protozoal disease with a chemical agent. "Chemotherapy may be defined as the prevention or treatment of disease by chemical disinfection or inhibition of the parasitic causes without marked or serious toxic effects." It is that branch of the science of biochemistry which deals with the therapeutic properties of certain chemicals in the curative and prophylactic treatment of parasitic diseases.

The chemical agent may be natural or synthetic. Thus quinine is as much a chemotherapeutic agent as arsphenamin. Location of the parasite does not affect the definition in any way. The parasite may be in the blood, in the lymph, in internal organs or tissues or on the external surface (skin and mucous membrane). Thus the term chemotherapy in the modern sense includes the treatment of syphilis by arsphenamin, the treatment of hookworm by carbon tetrachloride, the treatment of pneumococcal conjunctivitis by optochin or the treatment of ringworm with sulphur, the only essential factor is the complete routing or crippling of the parasites, no matter what their nature and location may be, without seriously damaging the cells of the body.

THEORIES OF PARASITOTROPISM AND ORGANOTROPISM

Side-chain theory. Ehrlich applied the same theory to explain parasitotropism and organotropism as he did to explain the theory of immunity. Kolmer gives the following extract from Ehrlich's Harben lectures.

"I also wish to lay special stress upon my view that the drugs are attracted by and bound to the protoplasm molecule by certain atom groups. I am inclined to look upon this as somewhat analogous to the binding of the toxins and of similar protein bodies. Yet on the other hand, there are fundamental differences between the two. For, as I have always insisted, the mode of binding the toxins is peculiar in so far as it is the result of a certain kind of assimilation which obviously consists in a process of a more or less synthetic nature. These toxin-receptors which produce immunity are bodies of a more independent character, and appear to be especially destined for purposes of assimilation. This high degree of independence is evidenced

by the fact that, in conformity with my side-chain theory, these receptors are very easily reproduced by the cell in excessive numbers, and after being separated from the cell, find their way into the blood.

I have now formed the opinion that in like manner a part of the chemically defined substance is attached to the cell by groups corresponding to these receptacles; these atom groupings I will distinguish from the toxin receptors by the name of 'chemo-receptors.' This view is more practically supported by the fact that an atoxyl-fast strain of trypanosomes is also resistant to a number of substances related to atoxyl, but otherwise showing widely different chemical characteristics. Evidently, therefore, the arsenic acid radical here represents the point of attack which is common to this series of substances. These 'chemo-receptors' must, however, be regarded as of a simpler structure than the toxin receptors. They do not show a similar degree of independence, nor can they be thrown off into the blood. The number of such chemo-receptors for poisons which trypanosomes possess represents the number of points of attack. By means of the resistant strains we can count off, one by one, these groups that are 'open to attack.'

This theory explains the affinity of a chemical agent or a drug for a parasite or a cell by supposing that there are certain special receptors on the cells to which these compounds become attached. Ehrlich's original work on the effect of various dyes and arsenicals on infective organisms, especially trypanosomes and spirochaetes, lent strong support to his hypothesis. According to him, a chemical agent cannot exert its action on the parasites, unless fixed by suitable chemo-receptors of the cells of the parasites. When arsenic or any other drug is administered, they are presumed to carry certain side-arms which are anchored to the special receptors of the cells of the organism. These side-arms have greater affinity for the receptors of the cells of the parasites than those of the tissues of the host, thus having a parasitotropic action with the least organotropic effect.

Chemical view. Although little can be said against Ehrlich's well-supported hypothesis, Kolmer is inclined to believe that it has prevented a chemical theory being worked out properly, and absence of a well-directed research in this line has considerably curtailed the rapid advance of chemotherapy in modern scientific direction. He is of opinion that the phenomena of parasitotropism and organotropism are purely chemical or physico-chemical in nature. He mentions Meyer and Goethliel's suggestion that arsenic produces its toxic effects by reacting with a substance which is present in the protoplasm in small amounts. Voegtlin and his co-workers have brought forward experimental data suggesting that the trivalent oxides of arsenic are specific poisons for the SH group of glutathione and possibly other SH compounds in the protoplasm of the cell, with a consequent sup-

pression of vital functions, which may explain the toxic and therapeutic effects of organic arsenicals like arsphenamin.

It will however be noted that the SH group in the protoplasm is present in the parasite as well as in the body cells. The special toxicity for the parasite is, therefore, explained by Voegtlin and his associates as being due to the difference in the absolute amount of SH groups in the protoplasm of the two, so that exposure to a certain concentration of arsenoxide will kill the parasite, while the cells of the animal will survive. They give a very plausible suggestion that those infective diseases, whose causative organisms require a considerable amount of SH group for their nutrition, will be benefited by arsenic. Voegtlin propounded an interesting theory depending upon the action of oxidation and reduction. He believes that the parasites maintain their oxygen by constantly exhibiting a reducing action on their surfaces. The body of the invaded host contains a protective substance which lies chiefly in the protein of serum. The colloidal particles of this protective substance are always striving to increase their surface oxygen which appears in the form of hydroxyl; if the protective substance has an excess of OH (hydroxyl) then it will neutralise the H-ion present on the surface of the parasite. This will therefore kill the parasite because it will not be able to maintain its H-ion the surface.

At present it seems justifiable to conclude that several factors are at work in producing the various parasitocidal effect of drugs. Cushney has summed up the present position very ably. He states that "these views have all been supported by a certain amount of evidence, and there is every reason to believe that these physical properties are important factors in the action of some drugs. But it is equally obvious that no one of them will explain the whole of pharmacological action, and there is reasonable doubt whether the whole of the physical characters taken together will suffice for this. From the present confusion the only legitimate conclusion seems to be that the activity of drugs depends on a large variety of factors, and that pharmacological action cannot be brought under any one law, either chemical or physical."

Factors influencing the action of drugs upon the parasites and the body cells. Attention has already been drawn to the different results obtained from *in vitro* and *in vivo* experiments. There is therefore some profound change occurring in the body which gives this divergence in the *in vitro* and *in vivo* experiments. The changes will mainly depend on the channels of absorption, for a variety of chemical and physico-chemical actions takes place before the drug is distributed through the body to act on the parasites it is meant to destroy.

After oral administration, hydrolysis, emulsification, saponification, etc., occur in the gastro-intestinal tract before the drug is absorbed into the circulation. After absorption, the detoxicating properties of

the internal organs, especially the liver, play an important part in the modification of the drug. The changes that occur after an intravenous injection are also important for, as the drug is directly introduced into the circulation, phenomena of lysis, agglutination, precipitation of proteins, etc., may occur. Important changes of oxidation and reduction may occur and a new compound may be evolved after combination with certain cellular constituents in the body.

After absorption the chemical agent is distributed in the body, not uniformly but selectively, and the aim of chemotherapy is to concentrate the agent in those tissues where the parasites are supposed to be numerous. The concentration in the tissues depends upon the method of administration, dose, elimination and the changes that occur in the body cells. Special affinity of a particular tissue will also determine the concentrations of the agent in the tissues.

Acquired or natural tolerance to the action of drugs is a well-known phenomenon. Certain individuals have got the power of tolerating large doses of poisonous drugs without showing toxic effects. In the case of habit-forming drugs, *e.g.*, alcohol, cocaine, nicotine, etc., the tolerance is probably psychic, developed as a result of the nervous system getting adapted to continued use. Other cases may be due to increased destruction of the poison, as is found with opium and its alkaloids, or the result of diminished absorption or increased elimination. Another conspicuous instance of tolerance is found in the formation of antitoxin. Such antitoxin formation is the result of repeated administration of foreign proteins, either animal or bacterial. Antitoxin formation has also been observed with certain glucosides, snake venom, poison ivy, etc.

DRUG RESISTANCE

It was not, however, known till very recently that parasites too acquire tolerance to drugs. This tolerance in parasites to withstand the destructive action of a chemical agent is known as *drug fastness*. A huge literature has since been piled up regarding the nature of drug fastness in various parasitic infections, such as trypanosomiasis, spirochaetosis, and from this standpoint the treatment of infectious diseases is of great interest in order to decide whether a particular remedy does or does not produce resistance in the causative organism. Ehrlich and his collaborators (1909) recorded interesting observations on the

drug fastness of trypanosomes. Working with nagana-infected mice they found that after feeding the mice with para-fuchsin, the parasites disappeared from the peripheral blood. After some time they reappeared, and by continuing the feeding it was observed that successive administration of the dye became less effective in removing the parasites from the peripheral circulation. Then a time was reached when the time of banishment of the parasites from the circulation became progressively shorter until the drug entirely failed to rid the blood of the organism. After transference of the strain to a healthy mouse it was found to be uninfluenced by the action of para-fuchsin. The drug had therefore produced in the organism a heightened resistance to withstand the otherwise fatal concentrations of the same drug. This interesting discovery was further supplemented by a series of experiments to determine the specific character of fastness acquired by trypanosomes with doses of various drugs. Arsacetin in doses insufficient to cure the animal of the infection with trypanosomes, developed in mice a strain of organisms which could not later be influenced even by maximum tolerated doses of the drug; the strain thus seemed to have acquired a 'fastness' to arsacetin. But it could be influenced by a more potent arsenical preparation, *e.g.*, arsenophenylglycine, which subsequently produced a further strain of resistant trypanosomes on repeated treatment with subeffective doses of this compound. This work of Ehrlich and others brought to light some very interesting facts about the specific character of drug fastness. It was at the same time observed that a strain of an organism resistant to the action of arsenic, may or may not show resistance to antimony preparations, *e.g.*, tartar emetic, but it never exhibited any fastness to trypanocidal dyes of the tetrazo series, *e.g.*, trypan red, trypan blue, or to triphenyl methane dyes (para-fuchsin). On the other hand, strains resistant to trypan red were also resistant to trypan blue, but not to the triphenyl methane dyes or to the arsenical compounds.

This characteristic resistances of the different micro-organisms to the action of various drugs has been observed not only in the case of trypanosomes but in various other infections. Thus Massart (1889) succeeded in making certain flagellates resistant to higher concentra-

tions of sodium chloride. Davenport and Neal (1896) were able to produce resistance to mercuric chloride and quinine in a protozoon (*Stentor coeruleus*) by exposing it for several days to the action of sublethal doses of those drugs. Danysz (1900) was successful in producing arsenic resistance in *anthrax bacilli* by cultivating them in a medium containing As_2O_3 . Morgenroth and Kaufmann (1912) found the pneumococci to have acquired resistance to ethyl hydrocupreine (optochin) when they were subjected to repeated sublethal doses. Shiga (1913) produced a strain of resistant cholera vibrio by cultivating the organisms *in vitro* in different concentrations of dyes, such as methylene blue, tryflavine, etc. The resistance of the vibrio gradually increased till it reached a maximum. Such resistance was, however, lost if the vibrio were cultivated in a medium not containing the dyes. Haelde and Baerthlein (1913) noted the resistance of typhoid and paratyphoid bacilli to quinine. Englin (1918) reported the resistance of *Plasmodium malariae* to quinine. Neuschlosz (1920) working with *Paramacium caudatum* was successful in producing strains of this organism resistant to the action of quinine, arsenic, antimony and various dyes.

The phenomenon of drug resistance has been observed by various workers both in experimental studies and clinically in the treatment of infectious diseases, and there is very little doubt that it does occur. The nature of this resistance is but imperfectly understood. It is one of the most complex biological phenomena that has been observed in the reaction of the living organisms to the action of chemicals.

The nature and mechanism of drug-resistance. It is very difficult to say at present why and how a certain strain of organism acquires the character of withstanding otherwise lethal doses of a poisonous drug. This resistance may be a character of the causative organism or it may reside in the tissues of the host. The idea that the resistance to the action of a drug is not a character of the infective organism but of the invaded host was first formulated by Breinl and Nierenstein, and by Mesnil and Brimont, who, working with trypanosomes, concluded that a strain of trypanosomes made resistant to the action of atoxyl in one species of host (mice) did not exhibit that resistance when transferred to another host (rat). But such a theory is no longer tenable as it has been established that a strain of trypanosomes in mice made resistant to an aromatic arsenical compound is similarly resistant when transferred to rats or rabbits and *vice versa*.

The question now arises as to what this peculiarity can be attributed. Ehrlich, in his side-chain theory, has postulated the existence of a large number of chemical groups in the protoplasm of the organism.

Each one of these chemo-receptors is supposed to fix a molecule of the drug by virtue of chemical combination, and according to this view, the influence of the host is negligible. He supposes that the phenomenon of resistance of a strain of organism to a particular group of drugs is due to a lower chemical affinity of the specific receptors for those drugs to which the strain has become resistant. Voegtlin and his co-workers in America have doubted the adequacy of this theory. They have experimentally proved that the action of arsenical compounds in trypanosomiasis is dependent on the active participation of the host. The parasitocidal effectiveness of chemical agents, such as the arsenicals, will therefore be determined to a considerable extent by the power of retention of the drugs by the host. They are of opinion that Ehrlich's theory is far too simple to explain the complicated phenomenon, considering the fact that a resistant strain of trypanosomes can be made to withstand 250 times as much reduced trypanamide as does the original strain. Voegtlin has therefore devised a theory which postulates that trypanosomes acquire resistance to arsenic by virtue of the development of an excess of sulphhydryl compounds, which enable them to detoxicate the poisonous effect of arsenic. Kolmer also supports a similar theory and explains the phenomenon on the basis of a chemical interaction between the drug and the parasite. He believes that natural tolerance is due to the absence in the protoplasm of the cell of the parasite of a chemical constituent capable of interaction with the drug administered, or the presence of a substance which unites with the drug and renders it inert.

Such a theory has, however, been criticised by Yorke (1931) who has shown that, contrary to the hypothesis of Voegtlin, the arsenic-resistant trypanosomes do not absorb any aromatic arsenicals even though these may be present in concentration rapidly fatal to the normal strain of parasites. By suspending normal trypanosomes in a nutrient medium containing 1 in 12,000,000 of reduced trypanamide for one hour at 37°C., it was found that all the drug was taken up by the parasites, while under the same condition the resistant strain did not absorb any drug at all.

Yorke is inclined to believe that the phenomenon may be explained in a different way. The adoption of the various micro-organisms to changed environments may be the result of natural selection, i.e., a gradual dying out of the more sensitive individuals and the survival of the more resistant ones. This is rather difficult to prove so far as drug resistance is concerned. But it must at the same time be admitted that different individuals of a strain differ in respect of age, and hence it is very likely that these may possess *per se* different degrees of viability. It is, therefore, justifiable to imagine that successive generations of a given strain possess greater power of resist-

ance than the original one. This theory, however, is not wide enough to explain the resistance that may be made to develop in some to an enormous extent. Another factor that may be working is a process of mutation or gradual adaptation in some or all of the parasites, whereby the successive generations acquire drug resistance, as a result of the stimulus of frequent exposures to sublethal concentrations of the drug. This process of mutation may be aided in some cases by a process of natural selection as well.

Drug resistance, specially in the case of trypanosomes and also in spirochaetal infection, is apparently a stable phenomenon independent of the kind of host in which the parasites may reside. Morphologically also the strains of resistant parasites are indistinguishable from the non-resistant ones. By repeated exposures to non-fatal concentrations of a particular drug they develop a certain characteristic by which no drug is absorbed by them, while the same concentrations would be fatal to the untreated organisms.

Drug resistance in trypanosomiasis. It has been known for a long time that trypanosomes which have survived the first effect of an arsenical compound, can later on withstand the effect of larger doses. Repeated arsenic medication produces in successive generations, a strain of parasites resistant to the action of arsenic. This has also been recognised clinically in sleeping sickness. The difficulty of curing trypanosomiasis in some cases with arsenical preparations is well known. In the treatment of Rhodesian sleeping sickness, doses of tryparsamide have been found to be ineffective in curing the infection, while maximum tolerated doses of Bayer 205 have been seen to produce a complete cure. This ineffectiveness of certain compounds in trypanosome infection is more readily seen in cases treated with insufficient doses of a particular drug, giving thereby a chance for the parasites to acquire a resistance to a particular chemotherapeutic agent.

The resistance of the trypanosomes against various arsenicals and dyes was first recognised by Ehrlich in 1908, since when many interesting phenomena have been brought to light in connection with the drug-fastness of trypanosomes. Voegtlin and others (1924) showed that arsenoxide (3-amino-4-oxyphenylarsenious oxide) was less effective in influencing the resistant strains of trypanosomes than the normal

strains when exposed to the same concentrations of arsenoxide. The behaviour of the parasites has also been found to differ with different preparations of arsenic. Arsphenamin, which is retained in the body after continued administration, can produce a sufficient degree of arsenic-resistance in a relatively short time. Other arsenicals such as atoxyl, arsacetin, tryparsamide and similar pentavalent compounds, which are rapidly excreted, take a much longer time to do the same. Yorke (1929) developed a technique of keeping alive suspensions of trypanosomes to study the trypanocidal property of various antimony and arsenic preparations. His strains of *T. rhodesiense* made resistant to atoxyl and acriflavine were tested *in vitro* and *in vivo* on (a) aromatic arsenical compounds such as atoxyl, tryparsamide, holarsol, arsacetin, reduced tryparsamide, reduced arsacetin, and novarseno-billon; (b) aromatic antimonials, such as stibosal and stibenyl; (c) the non-aromatic antimony and arsenic compounds, such as tartar emetic and sodium arsenite; (d) acriflavine and Bayer 205. Both the strains were found to be resistant to all the aromatic compounds of antimony and arsenic and to acriflavine but not to the non-aromatic compounds or to Bayer 205. It was also found that *in vitro* the resistance of the treated strains was much heightened compared to the normal ones. A concentration of 1 in 100,000,000 reduced tryparsamide killed a normal strain of *T. rhodesiense* within twenty-four hours, while under similar conditions a resistant strain withstood a solution of 1 in 400,000.

As the trypanosomes have been observed to acquire resistance, they have also been found to lose this drug-fastness after cyclical passage through different hosts. Werbitzki and Gonder (1911) found that an arsenophenylglycine-fast strain of *T. lewisi* lost the resisting character after passage through the rat louse. Morgenroth and Rosenthal (1911) observed gradual loss of resistance to arsenic in certain strains. Mesnil and Blanchard (1916) noted that passage through mice lessened the resistance of trypanosomes to human serum. Voegtlin and his co-workers (1924) reported that arsenic resistance can be reduced temporarily by passing a given strain through another mammalian host, such as rabbits and dogs. Yorke, however, by passing the resistant strains of *T. brucei* through the tsetse fly found that they preserved the resistant character unimpaired.

Whatever may be the specific character of drug-fastness in trypanosomiasis, the available evidence justifies the conclusion that it can be produced experimentally. But whether strains of resistant parasites develop in man during a course of treatment, it is difficult to say. There is no satisfactory evidence demonstrating the existence of these drug-proof trypanosomes in man. It has, however, been observed that drug resistance is

correlated with the chemical nature of the aromatic arsenicals. The pentavalent compounds of arsenic do not produce, as a rule, drug-fastness in trypanosomes to the same extent as do the trivalent compounds. A drug-resistant strain is more easily developed with arsphenamin than with neoarsphenamin. The chance of development of resistance is, moreover, dependent on the dosage, the quantity of drug administered and the timing of such treatment. If the doses are just below the quantity which will effect a cure, then repetition of such subcurative doses will help to produce a strain of drug-resistant trypanosomes. In this way, a strain can withstand several hundred times the dosage lethal to the normal parasites. In man such an occurrence may actually happen.

Drug-resistance in spirochaetosis. The existence of drug-resistant groups of spirochaetes is a matter about which little is known. After intermittent treatment with gradually increasing sublethal doses of arsenicals, spirochaetes are known to acquire resistance to the drug.

Margulies (1910) treated hens infected with *Treponema anserinum* with subeffective doses of salvarsan and after forty-six passages succeeded in producing in them a strain of these organisms, which could withstand double the original curative dose. Rothermundt and Dale (1911) could not, however, produce a resistant strain of *T. anserinum*. Gonder (1912), working with a Russian strain of *T. recurrentis* in mice, succeeded in producing a strain much more resistant than the original. Kritchewski (1927), in working with different strains of spirochaetes of relapsing fever in mice, found that certain strains could be sterilised with a maximum dose of salvarsan, while others proved very resistant. Akatsu and Noguchi (1917) were successful in increasing the tolerance of *T. microdentium* and *T. refringens* to increasing doses of various chemotherapeutic agents, such as salvarsan, neosalvarsan, bichloride of mercury, and iodine-potassium iodide solution (Lugol's solution) *in vitro*. Fe'dt (1932) produced a strain of *T. recurrentis* in mice, which could, after successive passages in the animal, withstand five times the original lethal dose. Likewise, the existence of solganol-fast strains is also recorded. There have been cases of failure with novarsenobillon in human relapsing fever recorded by several observers, though the drug has been recognised as a specific for the disease. There is thus evidence that such a thing as drug-resistant spirochaetes may occur.

In syphilis. It has been observed that certain cases of syphilis do not respond to mercury and iodide preparations. In

many countries the impression has been gaining ground that the results of treatment of syphilis with arsphenamin and similar preparations are not giving such promising results as in pre-War days. Silbersterin (1924) stated that it is becoming increasingly difficult to produce a negative Wassermann reaction in patients, though Moore and Robinson (1930) doubt the statement and attribute it more to the reaction of the individual to treatment than to the occurrence of arspenamine-fast strains of *T. pallidum*. The general trend of opinion in the treatment of syphilis is that the antisyphilitic remedies, such as salvarsan and neosalvarsan, have to be used in gradually increasing doses in order to obtain the maximum, parasito-tropic effect of the drug without the organotropic effect. If repeated subeffective doses are given, the chances of eradication of spirochaetes are less. This raises the question of arsenic resistance of the parasites, to avoid which Ehrlich advocated his doctrine of *therapia sterilisans magna*, but the latter is beset with practical difficulties.

The results of experimental work on this drug-fastness of Treponema to arsenic and various compounds are not at all confirmatory. Mergulies (1910) was unsuccessful in producing an arsenobenzene-fast strain of rabbit syphilis. Nichols (1911) in working with rabbit syphilis could not find any arsenic-fast properties in them after 4 exposures. In his series one relapse occurred, which is explained as being due to the drug not being able to reach the spirochaetes hidden in the tissues away from the site of action of the drug. Akatsu and Noguchi (1917) showed that *T. pallidum* increased its tolerance to salvarsan and neosalvarsan, in 3 to 4 months, to five and one-half times its original mark; against the action of bichloride of mercury the amount of increased tolerance was about 35-70 times the original and that the increased drug-fastness had a certain limit, beyond which no further advance could be made. Klauder (1924) could produce a strain of *T. pallidum*, whose resistance to arsenic was increased to a maximum of 68 per cent. with nine injections of ascending doses of arsphenamin, and after six transfers of the infection from one animal to the other.

In view of the aforesaid clinical and experimental data, it does not seem improbable that *T. pallidum* may acquire a certain degree of resistance to the action of arsenical compounds.

Drug-resistance in amœbic dysentery. With regard to amœbic dysentery there has been a strong belief that emetine-fast amœbæ occur. Experimentally, strains of *Entamœba histolytica* have been produced, which are fast to emetine and acriflavine. The inability to rid the patient of amœbæ even after maximum doses of emetine hydrochloride has been recognised by many clinicians in the treatment of chronic amœbic dysentery. To what this failure may be attributed, it is difficult to state at present. The transformation of the vegetative parasites to the cystic forms, alteration in the tissues of the host affording a chance for the parasites to ward off the action of a chemical, the peculiar character of drug-fastness of the strain, all or some of these, may contribute to the results. It has, however, been observed that cases resistant to emetine react normally to carbarsone, yatren or to other non-alkaloidal amœbicidal remedies.

Quinine-resistance in malaria. Similarly, resistant cases of malaria have been described by several workers. Inability to prevent relapse in many cases of plasmodium infection has been ascribed by many as due to the resistance of the parasites to quinine. James (1913), who investigated fully the subject of relapse, states that the failure of quinine therapy may be due to one of the following factors: (i) infection with different species of parasites, (ii) non-absorption of quinine from the gastro-intestinal tract, (iii) neglect to take the full dose, (iv) drug-resistance of the parasites. MacGilchrist (1915) could not, however, find any instance of quinine-resistance among his patients in India. Acton and others (1920) stated that a relapse for the fifth time could be equally controlled with quinine, with disappearance of the parasites from the peripheral blood.

The different strains of malarial parasites occurring in different parts of the world behave differently to quinine; the difference between endemic and epidemic malaria is widely recognised. James (1927), in a tentative trial of malaria therapy, used different strains of malarial parasites. It was found that the cases infected with Rome or Sardina strains were more severe than those infected with the Indian strains. The dose required

to control a primary attack of malaria caused by the former strains was about eight times greater than the dose required to control an attack caused by the latter. Also the effect of quinine was less marked in cases where the primary attacks were caused by the bites of many mosquitoes than when they were caused by the bites of one or two mosquitoes.

Whether quinine fails to rid the blood of malarial parasites owing to the acquisition of the property of drug-fastness on the part of the parasites or to some other causes, is not definitely known. Fletcher mentions a case of possible quinine-resistant malaria in a Tamil woman. Et. and Ed. Sargent (1921), in investigation on bird malaria, observed resistance to quinine in one of them and the parasites retained their resistant character even after passage through two other canaries.

Though quinine-resistant parasites may occur, the possibility of the development of this character in practical therapeutics seems to be small. Evidence available does not at present warrant the view that the failure of quinine treatment in some cases is due to the occurrence of quinine-resistant parasites. The mode and virulence of infection, the degree of susceptibility of the individual, the species and the geographical race of the parasites, are also to be taken into consideration in the alleged cases of failure with quinine. Faulty methods of administration and inadequate dosage may be responsible for many of the cases of failure. In addition, non-absorption of the alkaloid from the gastro-intestinal tract has also to be considered, before the existence of quinine-resistant parasites can be proved.

THE RETICULO-ENDOTHELIAL SYSTEM

Introduction. In recent years the reticulo-endothelial system has attracted a great deal of attention from workers interested in different branches of medical science. The anatomist, the physiologist, the pathologist, the hæmatologist and the immunologist have all evinced great interest in the study of this system and in the solution of one or more of its innumerable problems. The pharmacologist, who is interested in

obtaining a knowledge of the mechanism of action of drugs, has also been directing his attention to this system in the hope that a study of it might be helpful in furnishing answers to some of his problems. A perusal of the literature on the subject reveals that the efficacy of many drugs, including some of the so-called specific ones, may depend upon the functional efficiency of this system. The earlier view expressed by Ehrlich and others that the chemotherapeutic action of drugs depended entirely on their direct action on the causative agent of disease, has now few supporters. The accumulating evidence appears to be distinctly in favour of the view that drugs, in the majority of instances, act in an indirect way through the tissues of the body, and particularly through the cells of the reticulo-endothelial system. Time and further work alone can determine the exact role of this system in infection, immunity and chemotherapy. Incomplete though the knowledge may be at the present time, there seems to be very little doubt that the reticulo-endothelial system plays a part of great importance in recovery from diseases, more specially from those like typhoid fever, tuberculosis, spirochaetal infections, malaria, kala-azar and trypanosomiasis. In view of its increasing importance in tropical diseases, it seems necessary to give a brief description of the system, its accepted functions in health, and the part it plays in the cure of disease.

Definition. Widely scattered in the blood and tissues of man and other vertebrates, there are certain cells of mesenchymal origin and of the macrophage or large mono-nuclear type that possess the primitive capacity for phagocytosis and intracellular digestion. These take up all foreign particles that gain access to the body, whether they be inert or colloidal, inanimate or animate, bacterial or protozoal, and dispose of them in a manner best suited to the body economy. They collectively go by the name of the "reticulo-endothelial system."

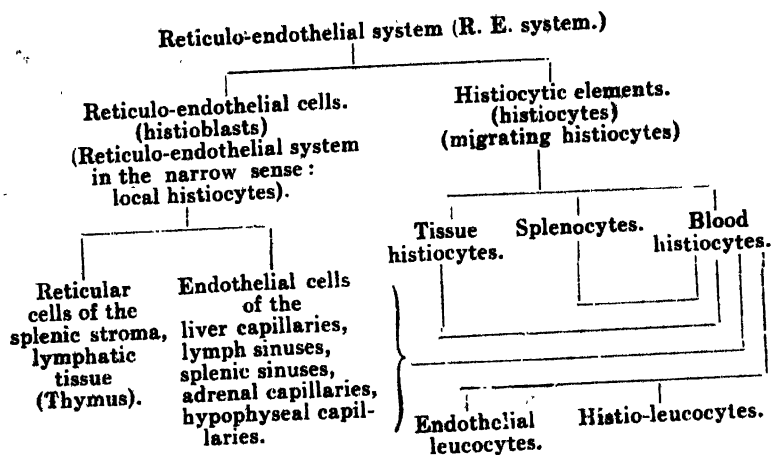
Evolution. The evolution of the reticulo-endothelial system is closely associated with the origin and development of parasitism and host-parasite adjustments. "In the long course of evolution of living things, it seems probable that the lower forms of life arose far in advance of the more highly differentiated forms. From the very moment of

their first appearance upon this earth the latter had to compete for their place in nature with a vast number of microbial forms. In the course of the adjustments necessitated by this complex communal existence, various forms of parasitism were established. In many instances invasion of a host by a parasite was fraught with danger, and as a defence against it, mechanisms of protection of different degrees of efficiency were developed. Even in the most primitive forms of life one or more simple means of self-defence are discernable; as the needs for self-preservation become greater the mechanism of defence also becomes more complex." (W. W. C. Topley). In the unicellular animal the function of protection is performed by the cell itself and is merely an adaptation of the ordinary feeding mechanism. In lowly organised metazoa this function is relegated to certain special cells. In higher vertebrates and in man these cells of protection are very highly differentiated and are distributed widely throughout the body, and go by the name of the reticulo-endothelial system.

Historical. The history of the recognition of the cells of the reticulo-endothelial system may be said to have begun about the end of the nineteenth century. Mallory's 'endothelial leucocytes' and Metschnikoff's 'macrophage cells' are now recognised to be reticulo-endothelial cells and these workers, therefore, may well claim to be the first to recognise and point out the importance of these cells. Several subsequent workers also met with these cells under various circumstances and referred to them under different names. In 1913, Aschoff and Landau proposed to group together these differently named cells into a single system and to call it 'the reticulo-endothelial system.' In 1924, Aschoff gave a detailed description of the anatomical distribution of the cells composing the system and pointed out their functional unity and stressed their immunological importance.

Distribution. The reticulo-endothelial cells have a very wide and scattered distribution throughout the body. They are to be found in organs, such as the spleen, liver, lymphoid tissue, bone-marrow, connective tissue, blood and endocrine glands. Amongst these organs, the spleen may be considered the largest store-house of these cells. The amount stored in the spleen as compared with other organs varies not only in different species of animals but also in different members of the same species. It has been found that after the removal of the spleen, regeneration of the reticulo-endothelial cells takes place more quickly and markedly in certain species of animals than in others. This has led to the presumption that the amount of reticulo-endothelial cells outside the spleen is also very variable and dependent upon the animal species. For the sake of clearness, the anatomical distribution of the cells of the reticulo-endothelial system as classified by Aschoff is given below in a tabular form.

CHEMOTHERAPY



Composition. Originally, Aschoff (1924) classified the cell elements of the reticulo-endothelial system into six groups according to the intensity of vital-staining and the size and compactness of the dye granules present in their cytoplasm. These groups are:—

- (a) The *endothelial cells* of the blood and lymph vessels.
- (b) The *fibrocytes* or ordinary connective tissue cells.
- (c) The *reticulum cells* of the splenic pulp and lymphoid tissue.
- (d) The blood *monocytes* and *splenocytes* [related to group (e) and (f).]
- (e) The *reticulo-endothelial cells* lining the sinuses of the spleen, bone marrow, adrenal cortex and hypophysis.
- (f) The *histiocytes* or the large phagocytic motile cells of the connective tissue.

Of these six types, the first and the second are the least phagocytic, the third and the fourth moderately phagocytic, and the fifth and sixth the most phagocytic.

The cells of the reticulo-endothelial system have been classified by Sabin into two main groups, namely, 'monocytes' and 'clasmatocytes.' The term 'histiocytes' is preferable to 'clasmatocytes.' Under normal conditions these two types of cells are found in all organs containing reticulo-endothelial cells. The ratio of monocytes to histiocytes in spleen puncture material is generally 6 to 1. In the peripheral blood, histiocytes are normally absent and the only representative of the reticulo-endothelial system is the monocyte. In pathological states and after experimental stimulation, histiocytes as well as all grades of intermediate forms have been found in the peripheral blood. These intermediate forms probably

represent stimulated monocytes with increased phagocytic power. The reticulo-endothelial system has come to be recognised now as composed of two closely allied cell types. These cells differ in morphology and possibly in function. The histiocytes are said to play the chief rôle in the phagocytic mechanism of defence, while the monocytes are more closely associated with antibody production.

Morphology. Normally, the two chief cell types composing the reticulo-endothelial system, as seen in supra-vital preparations, are quite distinct morphologically and can readily be distinguished from one another. Typical specimens of the two types may be seen in the blood of malarial cases twenty-four hours after an injection of quinine, or in the spleen juice of an advanced case of kala-azar prior to treatment. In these experimental and pathological conditions, some difficulty may be felt in classifying some of the forms intermediate between monocytes and histiocytes. With a little experience and discretion, this difficulty can easily be overcome. The following are some of the characteristics of the two cell types, in supra-vital preparations.

Monocyte. This cell is slightly larger than the lymphocyte, which it closely resembles. It has a big kidney-shaped nucleus with a deep and distinct indentation or 'hof' and shows the presence of a 'rosette' or clump of uniformly fine, neutral red particles at the 'hof' and a number of blue-staining mitochondria in its cytoplasm. Occasionally, a few small neutral red vacuoles may be seen in addition at the periphery of the cell. The chief characteristic for purposes of identification is the peculiar segregation of neutral red in the form of a 'rosette' of fine granules at the 'hof' of the nucleus. Even when the cell is stimulated and is showing increased phagocytic activity, this 'rosette' formation is noticeable; the only difference is that the 'rosette,' as well as the individual granules composing it, are very much bigger in the stimulated cell than in the normal cell. The presence of mitochondria helps to distinguish the cell from the histiocyte in which they are generally absent.

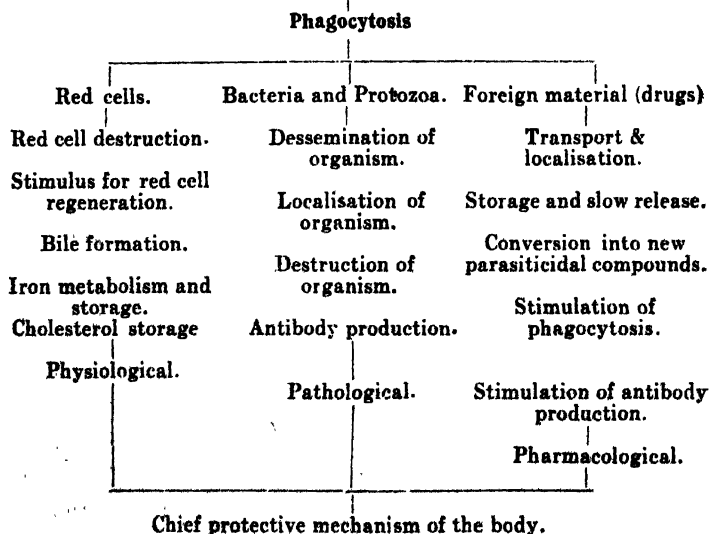
Histiocyte. This is a much larger cell than the monocyte; its nucleus is very variable in shape and differs from that of the monocyte by being small in comparison to the size of the cell, by being often oval rather than kidney-shaped and by occupying a more or less central rather than an eccentric position. The protoplasm of the histiocyte is somewhat granular, and mitochondria are generally absent, although occasionally, a cell may be seen with a few of them. The chief characteristic by which the cell is identified, is the way in which it segregates neutral red. Being very much more phagocytic than the monocyte, it takes up a larger amount of the vital dye and instead of segregating the dye in one place as the monocyte does, it distributes the dye diffusely in the form of large vacuoles in its cytoplasm. Another distinguishing feature noticeable, sometimes, is the presence of red blood corpuscles,

cell debris, platelets, within the cytoplasm. These are not always present, but when they are there, identification of the cell is much easier.

Functions of the Reticulo-Endothelial System

The reticulo-endothelial system performs a multiplicity of important functions both in health and in disease. We already stated that phagocytosis is the chief characteristic of the cells of this system and to it we may add that it is this property that helps it to perform almost all its functions. The best way to understand how that is done will be by tracing the sequence of events as they take place after phagocytosis of different materials. The substances that these cells are known to ingest may be divided broadly into three main groups, namely (a) red cells, (b) organisms, such as bacteria and protozoa, and (c) foreign materials, such as drugs. For the sake of clearness the results of phagocytosis of these substances have been classified in a tabular form and then discussed separately in detail.

Functions of the Reticulo-Endothelial System



Phagocytosis of Red Cells

Red cell destruction. It is an accepted fact that the cells of the reticulo-endothelial system take up for purposes of destruction those red cells whose allotted span of life is over and also those that get damaged by inflammatory processes, toxins or parasites. In such diseases

as malaria, kala-azar, typhoid fever, Weil's disease and poisoning by arseniuretted hydrogen in birds and phenyl hydrazine in dogs, phagocytosis of the damaged red cells can easily be observed. When hæmoglobin is injected into the circulation it is also taken up by these cells. *In vitro*, in tissue culture, the histiocytes have been observed to ingest red cells. Thus all observations made so far go to show that the histiocytes pick up old, damaged or dead red cells in order to destroy them. There appears to be no evidence, however, to suggest that they phagocytose healthy and young red cells.

Red cell regeneration. Under normal conditions red cell destruction and regeneration are in a state of equilibrium and this helps to maintain the red cell count at a constant level. The organ that is chiefly responsible for the control of the equilibrium appears to be the reticulo-endothelial system. The stimulus for red cell production is furnished by the histiocytic elements after they have ingested and digested the red cells. It has been shown that when there is functional failure of histiocytes, blood destruction is not followed by regeneration to any appreciable extent. It is, therefore, probable that the reticulo-endothelial system provides the stimulus for regeneration of red cells and that in the absence of such stimulus the bone marrow fails to produce a sufficient number of red cells to make up the loss sustained.

Bile pigment formation. The old view that hæmoglobin from destroyed red cells is brought to the liver and there gets converted by the glandular cells of that organ into bilirubin, is now recognised to be erroneous. McNee (1913), following upon Aschoff's description of the reticulo-endothelial system and as a result of some of his own experimental observations, suggested that the reticulo-endothelial system as a whole is responsible for bile formation. Subsequent workers clearly established, by extirpation of the liver and other experiments, that bile pigment is formed in all tissues in which reticulo-endothelial cells are present, including Kupffer's cells in the liver, but not by the glandular cells of that organ. Further confirmatory proof was obtained by the demonstration of bilirubin crystals within histiocytes after they had phagocytosed and destroyed the red cells. Therefore, all are agreed that one of the important functions of the reticulo-endothelial system is the elaboration of bilirubin.

Iron metabolism. One of the products of digestion of red cells and hæmoglobin is iron. There is increasing evidence to show that the reticulo-endothelial system is concerned in the metabolism and storage of this metal. In certain diseased states, such as pernicious anæmia, inanition of infants, toxic hæmolytic jaundice, malaria and after repeated injections of hæmoglobin, deposits of iron may be found in some of the cells of the reticulo-endothelial system. After splenectomy and experimental blockade of this system a marked disturbance of iron metabolism is often noticeable. It is highly probable, therefore,

that the system is of importance in the storage and metabolism of this metal.

Cholesterol metabolism. Storage of cholesterol appears to be another function of this system. Whenever there occurs an excess of cholesterol in the blood, either as a result of experimental cholesterol feeding or in certain diseases, such as diabetes, lipæmia, some cases of icterus and contracted kidney, the excess of cholesterol is taken up by the histiocytic elements of the liver, spleen and skin, and may be seen infiltrating these cells. The peculiar skin tumours at times seen in diabetics, (*Xanthoma diabeticorum*) are nothing but collections of histiocytes loaded with cholesterol esters and allied substances. These findings leave no doubt as regards the role of the system in cholesterol and lipid metabolisms.

Phagocytosis of Parasitic Organisms

Bacteria. As long ago as 1886 Wyssokowitsch showed that bacteria injected intravenously are taken up largely by the endothelial cells of the spleen. Werigo in 1894 injected anthrax bacilli into dogs and found the organism deposited in certain cells of the spleen, liver and lungs. Bull (1914-16) injected intravenously into rabbits and dogs living pneumococci and typhoid bacilli and demonstrated their presence shortly afterwards in organs rich in reticulo-endothelial cells, such as the spleen and liver. Wright, using virulent and non-virulent pneumococci, showed that within a few minutes of their introduction into the circulating blood, they were engulfed by the cells of the reticulo-endothelial system and conveyed to the internal organs. Durham, Buxton and Torrey (1906), Berry and Melick—all showed that bacteria injected into the peritoneal cavity were similarly engulfed by the cells of the reticulo-endothelial system and carried to internal organs, such as the liver and spleen, for purposes of destruction. The same phenomena were also observed after subcutaneous injection of living organisms. Although in the case of injections of pyogenic cocci the polymorphonuclear leucocytes phagocytose the organisms in larger numbers, evidence is not wanting that the reticulo-endothelial cells also play an important part in their removal. In addition to the above experimental evidence there is also proof of phagocytosis of organisms in many infectious diseases. Everyone is familiar with the presence of different bacterial organisms within macrophage cells in films of inflammatory exudates. In infectious diseases like pneumonia, typhoid fever, bacillary dysentery, tuberculosis, leprosy, actinomycosis and spirochætal diseases, the reticulo-endothelial cells may actually be seen loaded with these organisms in infected tissues. In all these diseases and in the granulomatous diseases, in particular, the characteristic cellular reaction is a proliferation and multiplication of the reticulo-endothelial cells, and the tubercle, the leproma and the gumma, are all formed as a result of this specific cellular

immunity reaction. The above evidence is convincing enough to prove that the reticulo-endothelial cells do phagocytose living bacteria that gain access to our bodies.

Protozoa. There is considerable evidence to show that the blood-inhabiting protozoa are also phagocytosed by the cells of the reticulo-endothelial system. As far back as 1898 MacCallum actually observed macrophage cells taking up malarial parasites in birds. All subsequent workers have corroborated this finding and have repeatedly found red cells and malarial parasites within the large mononuclear cells. Despite this, there are some who still believe that the cells of the reticulo-endothelial system take up only dead or dying malarial parasites. Recent observations in connection with the role of the reticulo-endothelial system in malaria have shown that the cells of the reticulo-endothelial system phagocytose living as well as dead malarial parasites (Krishnan, Napier and Lal, 1933). In kala-azar, oriental sore and dermal leishmaniasis *Leishmania donovani* are only found within the cells of the reticulo-endothelial system. Experimentally, when *L. donovani* are injected into susceptible animals, irrespective of their route of entry, subcutaneous, percutaneous, intravenous, intrapleural or intraperitoneal, they are picked up by the cells of the reticulo-endothelial system and carried to the spleen, liver and bone marrow. There they live and multiply within these cells. In Hepatozoon infections in cats, rats and squirrels, schizogony occurs in the mononuclear cells of the spleen and bone marrow and gametocytes are found in the circulating mononuclear cells. In trypanosome infections, although phagocytosis of the parasites has been observed, it does not appear to be a very pronounced feature. As regards phagocytosis of other protozoa by the reticulo-endothelial cells there is very little evidence. Taking the available data into consideration, we may say that the cells of the reticulo-endothelial system are capable of phagocytosing many of the blood-inhabiting protozoa.

Helminths. There is no evidence that the cells of the reticulo-endothelial system phagocytose helminthic worms that gain access to the blood or tissue. It is probable that they take up antigenic substances liberated from the worms, either during their life or after their death and disintegration, and lead to the production of antibody. What part this antibody plays in overcoming the helminthic infection it is not possible to say and as such the role of the reticulo-endothelial system in diseases due to worms still remains a mystery.

Fate of ingested organisms. Having shown that phagocytosis of bacteria and protozoa by reticulo-endothelial cells does occur, we may consider next the fate of the ingested organisms. Are they destroyed within the cells or do they live and multiply there? Both in the case of bacteria and protozoa, phagocytosis is not always followed by death of the ingested organisms. While it is true that large numbers of

them are killed by these cells, there is enough evidence to show that some of the organisms survive and even multiply within these cells. In the case of leishmania and hepatozoon infections, the parasites actually live and multiply within the reticulo-endothelial cells. Rous and Jones (1916) showed that certain bacterial organisms are found alive within phagocytes, and that the latter at times afford the bacteria protection from the injurious effects of serum antibodies in their environment. Bull (1916) showed that phagocytosis of pneumococci by reticulo-endothelial cells of partially-immune dogs resulted in the dissemination of the infection and the production of complications, such as meningitis and death of the animals. From the above evidence it is clear that phagocytosis and destruction are two separate functions of the cell and need not necessarily be present together at one and the same time. Depending upon the functional state of the cell, the nature of the organism ingested, and certain other factors, death may or may not occur after phagocytosis. It has been shown that one of the factors that helps to destroy parasites effectively is specific antibody. Although the importance and value of antibodies in different infectious diseases vary, being probably high in virus and certain bacterial infections, moderate in protozoal infections, and slight in helminthic infections, there is evidence that antibodies do sensitise all parasites in such a way that other destructive processes, such as phagocytosis and lysis, can carry on their functions more successfully. As antibodies are supposed to be a product of the reticulo-endothelial system, consideration of the views regarding their formation will be of interest.

Antibody production. The site of formation of antibody has been a disputed question for a considerable time. Years ago Metchnikoff suggested that the macrophages secrete some kind of ferment which help them to destroy the parasites that they ingest. Later, this view was given up, and the belief arose that antibody was elaborated by all tissues locally, at the site of inoculation of antigen. Recently, a large number of investigators studied this question and their work strongly indicates that formation of antibody takes place only in the reticulo-endothelial system. The splenectomy experiments of Hektoen and Curtis and the blockade experiments of Reiling and Isaac, Gay and Clark, Jungeblut and Berlot, are all in favour of this view. The most suggestive evidence, however, in this connection has been obtained by tissue culture work. Carrel and Ingebrigstson (1912) detected the presence of hæmopsonins and hæmolysins after the addition of goat's red cells to tissue culture of bone marrow and lymph glands from guinea pigs. Ludke (1912) confirmed their findings using ox and sheep corpuscles and showed, in addition, that agglutinins and lysins for typhoid and dysentery organisms could be obtained in a similar manner. More recently, Schiff (1928), Meyer and Loewenthal (1928), obtained bacteriolysins for cholera vibrios and typhoid bacilli by tissue culture methods.

From these and other data it is evident that an antigenic substance irrespective of its source or nature introduced into the animal tissue is taken up by the cells of the reticulo-endothelial system and removed to organs, such as the spleen and liver, where they stimulate the production of suitable antibody. Antibacterial, antitoxic and lytic antibody are all formed according to requirements.

Phagocytosis of foreign material. The chief characteristic of the reticulo-endothelial system that led to its discovery is phagocytosis of foreign substances. There is an enormous amount of evidence to show that its cells readily ingest substances like vital dyes, carbon, and Indian ink particles. If, for instance, one of these substances is injected intravenously into a rabbit and then films from spleen, liver and lung are examined, particles of the injected substances can be detected within the reticulo-endothelial cells. While very little difficulty is experienced in demonstrating the presence of inert and coloured particles, such as those mentioned above, the detection of soluble chemical substances (drugs) that are generally used in the treatment of disease, is a difficult matter. By the use of microchemical tests and special staining methods, colloidal and organic preparations of metals, such as iron, silver, antimony, bismuth and arsenic, have been shown to be present within the reticulo-endothelial cells. As regards the finding of alkaloidal and other drugs, *e.g.*, quinine within these cells, there is very little evidence; it is possible that they are also taken up by these cells and removed to the spleen, bone marrow, suprarenals and kidney. Until more work on these lines is performed it will not be possible to say which substances the reticulo-endothelial cells do and which they do not take up.

Regarding the disposal of particular substances after phagocytosis, there is evidence that the reticulo-endothelial cells in the course of their wandering, transport them to various organs and tissues (lung, liver, spleen, bone marrow and kidney), where they are either eliminated or stored. As regards the fate of soluble chemical substances very little is known; probably a considerable quantity is excreted within a short time through the normal channels of elimination and only a very small quantity is found in the body, possibly in the reticulo-endothelial cells. Here they are present either in their original state or in an altered form. As most of these foreign substances gain access to the body as drugs, at a time when it is in a diseased state, the question of prime importance is how they bring about cure and beneficial results and what part the reticulo-endothelial system plays in it. This brings us on to a consideration of the rôle of the system in chemotherapy.

Reticulo-Endothelial System in Chemotherapy

It is unfortunate that despite a large amount of experimental work very little progress has been made in the understanding of the mode of action of drugs in diseased states or of the role of the reticulo-endothelial system in pharmacotherapy. The reasons for this unsatisfactory state of affairs are not difficult to understand. In the case of virus and bacterial infections no drug has so far been discovered that can be called a specific, and in most instances the causative organism cannot easily be detected by direct examination of the blood or tissues. In the case of protozoal infections we, however, possess a knowledge about the specific action of some drugs. In addition, also the effect of these drugs upon the parasites can easily be studied. Being of far bigger size than bacteria and more easily demonstrable in the blood and tissues by direct examination of smears we can get a true picture of the effect of treatment on protozoa and on the course of infection, and we can also correlate these findings with various cytological and serological changes. This has enabled workers to tackle several of the problems in chemotherapy through investigations on protozoal infections, such as malaria, kala-azar and trypanosomiasis. A perusal of the studies conducted on these lines at the School of Tropical Medicine will show that very interesting and instructive results have been obtained. As regards helminthic infections the hindrances to progress have also been many and our knowledge of the mode of action of anthelmintic drugs is at present not very satisfactory. Nevertheless, taking the evidence as a whole, there appears to be very little doubt that chemotherapeutic action of drugs in general is not merely a simple direct action on the parasites. It may be true that in certain helminthic diseases, and possibly also in some protozoal infections, the action of specific drugs is predominantly a direct one, but with regard to the majority of other remedies, there is absolutely no evidence that they have any marked parasitocidal effect. It has repeatedly been shown that parasites are actually more vulnerable to drugs when they are brought into contact with them

within the body than outside it. Furthermore, drugs are rapidly excreted from the body and the dilution in which they occur in the blood and tissues after their administration in therapeutic doses is so very high that simple direct action alone can hardly be said to account for their efficiency. Blockade and splenectomy experiments have clearly established that dysfunction of the reticulo-endothelial system reduces and at times completely abolishes the therapeutic value of drugs. In view of these and other observations the consensus of opinion is that the reticulo-endothelial system plays an important part in chemotherapy. It would appear that in bringing about cure, the direct action of drugs on parasites is of the greatest importance in helminthic infestations, of moderate importance in protozoal infections, and of the least importance in virus and bacterial infections. As regards the importance of the reticulo-endothelial system in overcoming infections, the reverse order appears to be the most likely, *i.e.*, the system plays a part of slight importance in helminthic diseases, of moderate importance in protozoal diseases, and of the highest importance in bacterial and virus diseases. How far this view is correct time alone can decide.

Mode of action. When we take up for consideration the different ways in which the reticulo-endothelial system can possibly help drugs in bringing about a cure, four methods suggest themselves.

(1) That it acts as a store-house for the drug and releases it slowly as required—thereby preventing rapid elimination and ensuring continuous supply.

(2) That it carries the drug to the neighbourhood of lesions, where it is most needed.

(3) That it elaborates new compounds from the drug with greater parasitocidal power.

(4) That it is stimulated by the presence of the drug in circulation and thereby its functions of phagocytosis and antibody production become more pronounced and effective.

In support of the above view, we may cite the following evidence. Kritschtski (1928) showed that when germanin was

injected in a basis of 6 per cent. agar, its efficiency was greater on account of the slow rate of absorption of the drug from the agar which acted as a 'second spleen.' This supports the first contention.

Boyd, Napier and Roy (1931) showed that after injections of antimony compounds into monkeys, the highest concentration of the drug was found in the liver, where there was also a concentration of infection with *Leishmania*. It has also been experimentally shown that the reticulo-endothelial cells localise certain colloidal substances, especially those that carry a negative electric charge in inflamed tissue in preference to other tissues (Burrows, 1932). This clearly establishes the second contention.

Jiminez de Asua, Kuhn and Torino (1928), from a study of the action of arsenic compounds in splenectomised and non-splenectomised animals, have produced evidence to suggest that the reticulo-endothelial system is probably concerned in the conversion of these compounds into more efficient germicidal substances. The work of Jungeblut (1927) and Kristschewski (1927) support this work and all of them corroborate the third contention.

Krishnan (1933) has shown that the phagocytic function of the cells of the reticulo-endothelial system is stimulated by quinine in malaria and that this is partly responsible for the cure of the disease. It has also been shown by this worker that antibody formation is increased after antimony treatment of kala-azar and that this probably is responsible for cure. These observations lend support to the fourth contention.

Further evidence in support of the above can be obtained from a discussion of the mode of action of some of the important drugs used in the treatment of different infectious diseases. The following is a brief reference to some of them :—

Helminthic infections. The role of the reticulo-endothelial system in the chemotherapy of anthelmintic drugs is not fully understood. Although the evidence is strongly in favour of the mode of action of these drugs being a direct one on the worms themselves, there are suggestions in certain cases, that the beneficial results obtained may be attributable, in part at least, to an indirect action, which is dependent upon

the functional efficiency of the reticulo-endothelial system. This view appears to be supported, partly at least, by the results of treatment of helminthic infections of the blood and tissues. The actions of tartar emetic and emetine in the treatment of schistosomiasis, of atoxyl and antimony in filariasis, of gentian violet in clonorchiasis, and of tryparsamide in chyluria are in all probability indirect, through the reticulo-endothelial system. The dermal tests reported to be useful in the diagnosis of some helminthic infections, such as schistosomiasis, hydatid disease, trichiuriasis, filariasis and intestinal worms, are evidence of sensitisation to antigenic substances from the worms, and are most likely due to sessile antibodies elaborated by the reticulo-endothelial system. If it is so, then the system may be presumed to play some part in the cure of these infections. But at present we are not in a position to understand what exactly is the role of these antibodies in helminthic diseases. Further work on the subject can alone elucidate this point.

Protozoal infections. The role of the reticulo-endothelial system in the treatment of protozoal infections has been extensively studied. Although there are several drugs which may be called specifics and which are known to act indirectly through the reticulo-endothelial system, the mode of action of a few of the more important ones alone is discussed below.

Emetine. While there is evidence to show that the therapeutic efficiency of this drug in human amoebiasis is probably due to a direct action of the alkaloid upon *E. histolytica*, the work of Dale and Dobell clearly suggests "that emetine and the amoeba are not the only factors to be considered in the cure of dysentery and that the missing factor is probably the interaction between emetine and the host's tissues." If this is correct, then what other tissue of the host can play this important part more successfully than the ubiquitous reticulo-endothelial system? The available evidence does not suggest the way in which the system enhances or ensures the efficiency of the drug.

Quinine. The mode of action of quinine in malaria has been studied by different workers, and yet the views regarding

it are still very varied. While some believe that the drug attacks the parasites directly, others claim that it acts in an indirect manner through the host's tissues. Yorke and Macfie favour the view that antibodies play an important part in cure, while Taliaferro and Cannon (1931), Krishnan (1933) and others have obtained evidence that phagocytosis by cells of the reticulo-endothelial system is the chief factor in overcoming malarial infection. Recently, the large series of experiments carried out at the School of Tropical Medicine, Calcutta, have furnished strong evidence regarding the important part played by the reticulo-endothelial system in the cure of malaria. It has been shown that quinine, by accelerating the natural processes of mobilisation, proliferation and functional activation of phagocytic large mononuclear cells, brings about rapid engulfment and ultimate destruction of the malarial parasites. Whenever the drug fails to elicit the suitable reticulo-endothelial response, no improvement is noticeable, and after splenectomy of monkeys infected with *P. knowlesi* quinine fails to bring about the same degree of beneficial results as when the organ is present. These results leave no doubt that the reticulo-endothelial system plays a part of greatest importance in the cure of malaria by quinine. By this we do not mean that the direct action of the drug on parasites and infected red cells is of no consequence, for it has been shown that when the direct action is pronounced, it is very helpful in enhancing the phagocytic and destructive powers of the reticulo-endothelial system.

Antimony. The mechanism by which antimony destroys *Leishmania donovani* and brings about cure of kala-azar is still unknown. It is very doubtful that it is a direct parasitocidal action. Noguchi (1924) showed that tartar emetic has no action on *Leishmania donovani* cultures *in vitro*, and certain unpublished results of Napier and Halder also show that *Leishmania donovani* grows as luxuriantly in N. N. N. tubes, to which neostibosan and aminostiburea are added, as in control N. N. N. tubes. When antimony compounds are injected intravenously, they are excreted rapidly in the urine (30 to 40 per cent. within 24 hours, and over

80 per cent. within 72 hours); the dilution in which antimony is present during the short period of its stay in the circulation, is very high, and no direct action on the parasites can possibly be conceived of, in such low dilutions. The opinion that its action is through the tissues of the body is, therefore, fast gaining strength. Brahmachari (1928) suggested that probably urea stibamine is converted into a trivalent oxide of antimony by the host's tissues in a manner similar to what happens in the case of compounds of arsenic and that this oxide is more parasitotropic. It is no doubt true that some of the antimony injected is taken up by the cells of the reticulo-endothelial system, but there is no certain evidence either of its conversion into stiboxyl or of the latter's higher parasitocidal properties. In experimental kala-azar in animals, such as mice and hamsters, it has been repeatedly shown that antimony fails to bring about cure of their infection. The 'clasmatocytes' that are supposed to effect the transformation of the drug to stiboxyl are present in them, and there is also evidence that these cells take up the injected antimony. Why then do they not convert the drug into the oxide and bring about the death of the leishmania parasites in them? Acton and Chopra (1927), and Chopra and Das Gupta (1929), found that when antimony compounds are injected intravenously into kala-azar patients, it causes enlargement and rhythmic contractions of the liver and spleen and that this is due to an increased functional activity of the adrenals. This observation led them to suggest that the alteration in the permeability of the vascular walls brought about by the hyper-activity of the adrenals caused a diminution in the permeability of the cells of the reticulo-endothelial system and this in turn led to the starvation and death of the leishmania parasites present in them. Krishnan (1930) confirmed these findings in an indirect manner by studying the changes in the leucocyte picture after adrenalin injection into kala-azar cases, before, during, and after, treatment. This work clearly indicated that a condition of hypoadrenia existed in kala-azar cases and that treatment helped to bring about a normal condition. But what part this alteration in the adrenalin

content played in overcoming the infection could not be clearly determined. In continuation of this work Napier, Krishnan and Lal (1933) conducted certain cytological studies on kala-azar patients with the help of supravital staining technique and showed the importance of the reticulo-endothelial system in infection and immunity in kala-azar. It was found that within the animal body, *Leishmania donovani* are present only within histiocytes and that in untreated kala-azar cases there is an enormous increase in the histiocytic elements of the reticulo-endothelial system and a reversal of the normal monocyte-histiocyte ratio. During and after treatment a distinct drop in the number of histiocytes is noticeable and this is followed by a gradual restoration of the monocyte-histiocyte ratio to normal. Whenever antimony failed to bring about these cellular changes, the patient showed no clinical improvement. In experimental kala-azar in animals, such as mice and hamsters, the same sort of reduction in the number of histiocytes took place after treatment, but it was not followed by a rise in the monocytic elements. On the other hand, the histiocytes rapidly proliferated again and led to an intensification of the infection. This appears to suggest that the action of antimony in kala-azar is an indirect one through the reticulo-endothelial system. The impression gained is that three factors are at work in this indirect action, namely, (a) reduction in the number of histiocytes, within which alone the leishmania seem to live and multiply, (b) proliferation of monocytes leading probably to antibody production, (c) destruction of leishmania by lytic antibodies. The first (a) is probably due to alterations in cell permeability as suggested by Acton and Chopra, leading to their disintegration, and as regards (b) and (c) there is evidence that antibodies are formed in kala-azar, that they are associated with proliferation of monocytes and that they are capable of destroying leishmania, both *in vitro* and *in vivo*.

Arsenic. Various compounds of arsenic are used in the treatment of trypanosomiasis and spirochaetal infections. The mode of action of these preparations seems to be an

indirect one, like that of antimony compounds. The presence of arsenic within the reticulo-endothelial cells has actually been demonstrated by the silver impregnation method by Jiminez de Ausa and Kuhn (1928). Splenectomy experiments in spirochaetal infections have demonstrated that infections held in check in animals break out into acute manifestations in splenectomised animals and that treatment of these with specific drugs is not as effective as in non-splenectomised animals. Kritschewski and his colleagues (1927-28) have produced evidence to show that the mortality rate is increased and the cure rate greatly decreased after splenectomy and that an intact reticulo-endothelial system is necessary for the full therapeutic activity of compounds of arsenic. From these and other observations it may be suggested that the reticulo-endothelial system functions, (a) by serving as a depot for concentrating arsenical drugs, (b) by helping in the production of more efficient parasitocidal substances and (c) by increasing the amount of antibody produced and by bringing about destruction of parasites.

The control of immunity through the reticulo-endothelial system and the chemotherapy of syphilis has received much attention during recent years. It is probable that many of the prophylactic and therapeutic measures used in combating the toxic effect of arsphenamine have their seat of action in protecting or allaying the cells of this system. The reticulo-endothelial system through its property of phagocytosis is an important agent in the purifying mechanism of the blood, and it is also considered to be the chief source of antibody production. It is considered to be of great importance in intravenous therapy, for many materials injected into the blood-stream disappear from it quickly with deposition in the reticulo-endothelial cells.

Reticulo-endothelial system is believed to be bilirubin-producing apparatus. Marked bili-rubinæmia indicates hyperfunction of the reticulo-endothelial system and hypo-function of the liver, caused by the toxic action of either the syphilitic virus or the arsphenamine. This system plays an important role in the struggle against syphilitic infection, and the arsphenamine reaction as a group are largely referable to centres for localisation of reticulo-endothelial system in the liver, the suprarenal glands, the bone marrow, the capillary endothelium and the skin. Measures aimed at the protection of this system are important in the prevention of reaction to arsphenamine.

Bacterial and Virus infections

In bacterial and virus diseases no drug has so far been discovered that has any specific action on the causative organism and, therefore, our knowledge of the chemotherapeutic action of drugs used in these diseases is still very unsatisfactory. The beneficial results that are obtained in these diseases are chiefly dependent upon the natural resources of the body to combat disease. The best we can do in these infections, therefore, is to help the natural process at work, in one way or another. This has been attempted with a certain degree of success.

In the case of chronic infections, a large number of protein substances such as peptone, milk, muscle extract, vaccines and sera, and certain colloidal metals have been used to stimulate the natural responses of the body. Although our knowledge as to how these substances act is still very vague, yet there are reasons to believe that the therapeutic results obtained are probably attributable to a non-specific stimulation of the reticulo-endothelial system by these substances. It has been shown that serological alterations such as increase in titre of antibodies, and cellular changes such as leucocytosis and increased phagocytic activity of mononuclear cells, are noticeable after injections of these non-specific protein substances. There is evidence that these substances are concentrated in organs such as the liver, spleen and bone marrow; it is likely that through these organs an increase in the efficiency of the natural immune processes occurs.

The action of specific anti-sera used in the treatment of acute infections is chiefly a direct one upon the causative agent of disease. They either destroy the agents themselves or prepare them in such a way that other mechanisms of protection may destroy them subsequently. Specific vaccines, when injected into the body, are picked up by the reticulo-endothelial cells and result in the formation of specific antibodies which act as described above.

Conclusion. By way of conclusion we may state that evidence obtained from studies on the mode of action of drugs in

infectious diseases taken as a whole, strongly suggests that in the overcoming of infections the reticulo-endothelial system plays a part of no mean importance. The exact manner in which the system responds to the stimulus of treatment appears to depend upon the nature of the infective agent concerned. While certain parasites are readily destroyed by phagocytes, others require to be disposed of by the destructive action of lytic anti-bodies. The ideal response in the first case is a mobilisation and functional activation of the phagocytic cells of the reticulo-endothelial system, whereas in the second instance the best results are obtainable by increased antibody production. When either of these methods fails, the reticulo-endothelial system attempts to utilise other methods at its command, such as elaboration of powerful parasitocidal substances from the drugs used. From this there is every reason to believe that beneficial results of drugs are not due to one single factor but rather to a combination of factors. Which one of these factors plays the predominant part varies in each case. The specific drug is that which is capable of stimulating the natural processes concerned in the cure of disease, and in addition bringing about such changes by direct and indirect action on the parasite or its environment, as would be conducive to the success of the natural processes at work. If this is so, then it is easy to understand that a knowledge of the reticulo-endothelial system, which is the chief protective mechanism of the body, is essential not only for the proper understanding of infectious diseases, but also for the carrying out of successful treatment.

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CHAPTER VI

PHYSIOTHERAPY

Physiotherapy is derived from a Greek word meaning 'nature cure' and is defined as "the use of natural forces, such as light, heat, air, water, and exercise in the treatment of disease." Probably the oldest forms of physical therapy are massage and the so-called "healing waters" or hydrotherapy. Light and heat therapy have been gradually introduced; during the past fifty years, electricity and radium have been added to this group.

The use of physical methods in therapy has received considerable attention of late years. As these methods are being employed with success in various diseases commonly occurring in the tropics it will not be out of place to briefly discuss them here.

HYDROTHERAPY

This term is used to denote the therapeutic procedures dealing with the external application of water at different temperatures over the whole or a part of the body. Hydrotherapeutic measures have been known for a very long time but were formerly practised on a purely empirical basis. It is, however, now possible to explain the fundamental principles involved in them from a physiological standpoint.

Indications. There are very few diseases in which hydrotherapy in some form or other is not capable of rendering some service. Hydrotherapy finds its chief application in diseases of the nervous system where it is perhaps more important than many medicinal agents. It has been employed from time to time for its sedative, tonic and antiphlogistic effects. The sedative effects are, however, the most important from the point of view of the physicians. In many circulatory diseases, the value of hydrotherapy has been more than once recognised. In cardiac neurosis and pseudo-angina, hydrotherapy has been widely used.

In respiratory diseases, its field of utility is well known. It has been employed whenever an antithermic, decongestive and antiphlogistic effects are sought. As a respiratory exercise, cold effusion or immersion of the face in cold water has been recommended. In cases of obesity, gout and other disorders of metabolism, hydrotherapy, combined with massage, has been found of great value.

Effects produced on the system. The main object of this therapeutic measure is to obtain a reaction in some definite direction and to serve some definite purpose. The effects produced are varied according to the temperature of the water used for the bath and may be classified under the following heads :—

A. *On the nervous system.* A tonic and stimulant action is produced in cases of depression, of sluggish function and of low blood pressure; a sedative and soothing effect is obtained in irritability of the nervous system. In cases of meningitis, cerebral hyperæmia, etc., an antiphlogistic effect is also said to be produced.

B. *On the circulatory system.* In the first stage, a peripheral vaso-constriction is produced with pallor and cooling of the skin. This effect lasts only for a short time. In the second stage a more prolonged effect is produced in the form of vaso-dilatation with a red flush of the skin and a sensation of warmth. The blood stream can be markedly influenced by hydrotherapeutic measures. The Vienna School of Winternitz has proved by tests on healthy human beings that cold baths of a short duration with friction or rubbing produce an increase from one million to one million and a half of erythrocytes and treble the number of leucocytes. They increase the hæmoglobin by 20 to 25 per cent.

Excessive cold produces local anæmia and if prolonged, ischæmia and death of tissues. Heat also acts in a similar manner. Short application of heat produces a local increase in the constituents of blood. By the application of stimulating measures to one area of the body, the blood can be diverted to this area and in this way congestion of other parts is relieved. Thus the use of the abdominal compress or girdle will reflexly relieve a congestive headache.

C. *On the respiratory system.* An increase in depth is always observed, and the rate is also somewhat increased.

D. *On the urinary system.* A temporary diuresis is produced.

The application of baths, hot or cold, should be followed immediately by reaction, in normal individuals. In the weak and feeble this reaction is delayed. If it does not occur or is incomplete the application of baths is inappropriate and should be modified. The reaction may be hastened by the application of cold after heat, by friction in the bath and by using chemical stimulants such as CO_2 and various chlorides in the water.

Hydrotherapeutic Measures

Compresses. **Hot compress:** This is very commonly applied in all kinds of inflammatory conditions. The method is very simple but should not be used indiscriminately. Unless used carefully, hot compresses in acute inflammatory conditions of a joint often bring about an impairment of function. Compresses should be applied as hot as the patient can bear and must be kept hot by frequent changes. They produce a local hyperæmia and, therefore, should never be applied to fresh injuries. They are efficacious in relieving spasm.

Cold compress. These are less frequently used. Due to the vaso-constrictor action of cold a beneficial effect is produced on recent injuries and inflammations.

Packs. **Hot pack.** These are used to facilitate elimination of toxins from the system. The water must be as hot as possible as the sheet taken out of the hot water cools off very quickly.

Cold packs. For the cold pack the water should be about 75°F. or less. The colder the water, the better the reaction. The wet pack has a very relaxing effect on the nervous system. It has been used very successfully on maniacs and in cases of chorea. The duration of the treatment is one hour but the treatment should be interrupted if the patient complains of chilliness.

Baths. Baths are of two different kinds—the hot bath and the cold bath. A good deal of confusion exists with regard to the temperature of the water used in the different forms of baths commonly employed. The following table will be useful.

Cold bath	..	40°—65°F	(4.4°—18.3°C). .
Cool bath	...	65°—75°F	(18.3°—23.8°C).
Tepid bath	...	85°—95°F	(29.4°—35.0°C).
Warm bath	...	95°—100°F	(35.0°—37.7°C).
Hot bath	..	100°—110°F	(37.7°—43.3°C).
Very hot bath	...	100°—120°F	(43.3°—48.8°C).

Cold bath. Cold baths are used to bring down the temperature in those fevers where antipyretics are not advisable. When using cold baths, two opposing factors must be considered. The colder the water the more rapid the passage of heat from the body surface, but cold water will also produce constriction of the cutaneous vessels and in this way the passage of heat from the interior of the body to the skin will be delayed. A balance must, therefore, be struck and in practice it is found that baths at about 69.8°F. or 21°C., are most efficacious in reducing temperature. The temperature once depressed does not rise again at once but remains low for hours. Cold baths are sometimes inconvenient from the point of view of the patient. In such cases cold sponging may be employed as it has a similar effect to cold baths and stimulates the nervous system. In typhoid fever when the temperature rises above 103°F., cold applications in the form of sponging are advisable and this should always be accompanied by friction of the skin which not only prevents chilling but also dilates the cutaneous vessels. During the initial stages of the fever the reduction of temperature is transient and slight. In the third week of the disease, however, when the temperature is beginning to show wider diurnal fluctuations, baths usually produce a much more marked and prolonged remission. Furthermore the remissions are most marked at times when the febrile temperature has a downward tendency.

Antipyretic drugs and cold baths in fever. A word may here be said about the relative value of antipyretic drugs and cold baths. Both these have their respective advantages and disadvantages. The chief advantage of a cold bath is that there is no danger of collapse, but this need not be apprehended if a proper drug is selected and the dose properly adjusted. The drugs may save the patient the exertion, discomfort and the shock which are attendant on a cold bath. In the case of baths, the temperature-regulating mechanism is not adjusted to normal and the patient feels all the ordinary effects of an attempt to reduce the temperature below normal, *i.e.*, chill, cyanosis, etc., and the metabolism is increased rather than decreased. The action of chemical antipyretics is more pronounced and lasting and resembles more closely that of natural defervescence. Barbour and his associates have shown that antipyretic drugs bring about dilution of the blood, which favours the dissipation of heat by radiation. Besides this their analgesic action is of great value in influencing the subjective condition of the patient.

The disadvantages of cold baths are greatly diminished if tepid baths are used. Although these have not such a marked antipyretic action, they have a more stimulant action, improve the blood pressure and digestion and promote sleep. The nitrogen excretion is increased. In prolonged fevers such as typhoid, antipyretic drugs should never be used nor should they be combined with cold baths as they prevent the only thing which is essential, that is the reaction. The excretion of

antipyretic drugs takes place from the already overstrained kidneys in constant fevers, while the already disturbed stomach is irritated by their use. Antipyretic drugs further decrease oxidation and may interfere with the ordinary protective efforts of the body against disease. Besides, the fever will sometimes resist all doses of antipyretic drugs which can be given safely, while the temperature can be lowered by cold sponging or a bath. In septic fevers and tuberculosis antipyretics do harm by depressing the patient and producing increased perspiration. In these conditions cold bathing serves no useful purpose as the patient shows no reaction. In acute illness if the application of cold is impossible, these remedies may be given, but usually they are unnecessary, as unless the fever is prolonged it is not harmful. If these drugs are used they should never be pushed till toxic symptoms such as cyanosis are produced. If given in moderate doses they do not produce the desired effect, cold baths should be applied. In thermic fevers such as heat stroke, antipyretics are useless as they do not stop the rapid rise of temperature.

Hot bath. Exposure to mild degrees of heat, causes a dilatation of superficial vessels; but some compensation is attained through constriction of deeper vessels. The circulation rate is increased by about 29 per cent. It tends to decrease the load on the heart to a minimum. Exposure to higher temperatures, on the other hand, temporarily increases the work of the heart, possibly 30 or 50 per cent. or even more, but ultimately the subject gains. Such measures are desirable in some cases of circulatory disorders and they may prove useful by ridding the body of fluid or toxins through sweating.

Hot baths are indicated whenever elimination is desired and especially when kidney function is defective. They are used in various schemes of hydrotherapy in order to act upon the foci of inflammatory trouble, *e.g.*, in general muscular rheumatism and fibrositis, the heat of the bath helps to relax the parts thereby restoring them to a healthy function. The use of these baths in cases of anaemia is also indicated. These baths are contraindicated in all forms of heart disease, in general weakness and when there is inclination to hæmorrhage. Plain water may be utilised for this purpose, or hot mud and peat baths. Massage is sometimes very useful along with these baths.

Generally, various methods of hot air or vapour baths are available of which the following may be mentioned as being the most common:—

Turkish baths. These consist in the exposure of the unclothed body to dry heat at varying temperature (up to 250°F. or more) for 20-30 minutes. By this means abundant perspiration is induced and thereby toxins are eliminated. It is followed by massage, douching, and rest for an hour or so during which an abundance of plain water should be drunk.

Russian baths. These are very similar, but the air is saturated with water vapour and, therefore, the temperature cannot range so high. Perspiration is induced more rapidly, and the bath is of shorter duration.

In both of these the object is to induce rapid elimination of toxins and other poisons and at the same time to assist in maintaining the free mobility and function of the various parts of the body by massage. Either may be used advantageously as a routine preventive of gout or rheumatism, especially by those who are unable to secure suitable exercise.

Spray bath. Application through a large perforator or rose nozzle of a continual fresh layer of water in a finely divided state with a certain mechanical impact on the skin constitute the main principle of spray baths. This removes secretion and has a marked sedative effect on the nerves. It is very useful in sunstroke, either alone or combined with ice rubbing; in typhoid fever the combination is especially efficient.

Tepid sponging. This is best given late in the afternoon or towards evening, the water used being at about 65°F. The face and neck are first dealt with by applying cold compress at 60°F. to the head after sponging. Sponge downwards exposing only the part being sponged. After the whole body has been gone over, the patient is dried thoroughly, wrapped in warm blankets and left for an hour or so. A moderately sedative effect with abstraction of considerable heat is produced by these means. They are particularly indicated for old people with arteriosclerosis in whom a strong stimulus must be avoided and who need a stimulation of the peripheral vascular system. They are useful in febrile cases who are too sick to be moved about and they can be repeated any number of times.

Medicated baths. Medicinal agents in some form or other may be mixed in the baths. It is not definitely known whether these produce any special effects though positive claims have been made by various workers. Alkaline baths, sulphur baths, etc., have been frequently employed for these purposes.

MINERAL WATERS

The therapeutic qualities of mineral waters have never been fully appreciated by the medical profession in India though their virtues have been empirically known for a long time. In England and on the Continent of Europe, famous spas have developed by the side of hot and mineral-water springs and people are taking advantage of their healing effects. No rational explanation was given regarding the properties attributed to these waters. Since the discovery of radium, however, it has been contended that some of these waters are radio-active, which may probably explain their physiological activity. Others assert that the presence of traces of rare elements in these waters is responsible for their action. Recently, a hormone of the nature

of œstrin is said to have been found in the mud spas like Frazenbad and it is likely that other hormones may be present. Different kinds of enzymes have also been detected. Besides the hygienic and climatic factors all these various ingredients of the soil occurring in solution are responsible for the therapeutic effects produced by these spas.

For the treatment of tropical invalids suitable spas should be selected. The following points may be carefully considered :

1. *Climate.* A good sunshine record is essential, with protection from cold winds.

2. *Altitude.* This, for the majority of patients, should be several hundred feet above the sea-level.

3. *Sub-soil.* Adequate drainage is essential if chills are to be avoided and patients enabled to be as much in the open air as their condition permits.

4. *Waters.* These must be suitable for the treatment of intestinal complaints, derangements of the liver and other digestive organs and for restitution of the blood-forming organs.

5. There should be abundant facilities for recreation and exercise which play a very important part during spa-treatment.

Therapeutic effects of mineral waters. The radio-active thermal waters are remarkable for their low mineral content, but the mineral elements are in a high degree of ionic dissociation and possess different chemical activity from that produced by artificially produced solutions of the same salts. Diuresis is the most conspicuous effect of drinking these waters, and is much greater and more rapidly produced than with a similar quantity of distilled water, a fact which has been frequently demonstrated by experiment. The chlorides, urea, uric acid, etc., are also excreted in increased amounts. In gout, mobilisation of the stored up uric acid occurs, and it appears during the first few days of treatment in increased quantities in the blood, with the result that an acute attack of gout is not uncommon when treatment is started. Later, the blood uric acid falls, and a long period of freedom from attack follows. The chief sphere of usefulness of the radio-active thermal waters is in gout, subacute rheumatism, fibrositis and neuritis.

The muriated or sodium chloride waters, with the addition either of carbon dioxide, bicarbonate of soda, the sulphates of sodium, calcium and magnesium, or sulphur, are mainly used in the treatment of digestive disorders. The principal diseases of the digestive tract which are successfully treated include the various functional dyspepsias, reflex dyspepsias (from cholecystitis, gall-stones, chronic appendicitis, etc.), chronic catarrh of the stomach, early cirrhosis of the liver, constipation and irritable conditions of the colon. The alkaline waters enjoy a great reputation in the treatment of catarrhal states, but are contraindicated in atonic dyspepsias. Carbon dioxide and sodium chloride (muriated) alone have been found to increase the secretory activity of the stomach, whereas the sulphated alkaline waters of Karlsbad and Marinebad, in spite of their carbon dioxide and sodium chloride content, tend to diminish it. It thus follows that in disorders associated with hyperchlorhydria and hypertonia, the simple alkaline and sulphated alkaline waters are indicated, whereas in the opposite condition the best results will be obtained from simple gaseous waters (radio-active), or very weak muriated, or muriated alkaline ones. In the nervous dyspepsias, the exact action of the water on the secretion is of little importance compared with its general tonic and stimulating influences.

In the treatment of liver disorders, which include congestion and enlargement, due to over-eating, alcohol, cardiac failure, malaria, cholelithiasis, cholecystitis, catarrhal jaundice, and that undefined disorder biliousness, which has a very real existence in general practice, the muriated waters, both alkaline and sulphated, and the sulphur waters, are used. They all tend to dilute the bile, promote a free flow, and dislodge concretions.

The stronger muriated and sulphated waters are not as a rule taken at spas, but are bottled and exported for use in the patient's home. By their hydragogue and cathartic action they are indicated in cases of congestion, and produce free watery stools, but they should never be used in cases of catarrh of the bowels.

Chronic diarrhoea (often of tropical origin) will usually benefit from suitable spa treatment. When associated with portal congestion, the mildly aperient waters of Cheltenham and Leamington are particularly indicated, while in other cases, the simple thermal, sulphur or calcareous waters will produce better results.

Chronic constipation is extensively treated by mineral waters. The strong sulphated and muriated waters should only be used in stout plethoric individuals, since they produce free watery evacuations and deplete the portal system. In persons of weaker physique, the milder muriated and sulphur waters are to be preferred. They are usually prescribed before breakfast, and followed by a short walk.

Hæmorrhoids are often treated by mild aperient waters, but they are said to respond particularly well to sulphur waters, and the wide use of sulphur therapeutically in this common complaint would appear to support the claim. The sulphur waters, also owe their aperient action largely to the other mineral constituents present. The sulphur present is considered to exert a special action upon the liver. The weaker sulphur waters have an aperient action only when taken in large quantities; this again being due to the action of the salts present. Otherwise, they are merely solutions of sulphuretted hydrogen and carbon dioxide.

Where the simple alkaline waters are not available their place is taken with equal advantage in most cases by the alkaline muriated water. They contain sodium bicarbonate with varying quantities of CO_2 . They are diuretic and are useful in gout, glycosuria, dyspepsia of the hypertonic type and in liver disorders.

The chalybeate waters are of two chief kinds, the one containing carbonate of iron, and the other sulphate of iron. These chalybeate waters are easily assimilable, are not constipating, and so are valuable in the treatment of dyspepsias due to anæmia and debility. They might with advantage be more widely used.

It is usual for mineral waters to be taken on an empty stomach and where an action on the stomach or bowel is

important, the chief drinking is done before breakfast. The dose will vary with the strength and character of the water, the type of patient and malady to be treated, and is usually from half a tumbler to five or six tumblers. Later, in the day, the same or other mineral waters may be taken according to the resources or custom of the spa. For instance, an aperient water may be taken before breakfast, and a mild saline to stimulate the gastric functions before lunch and dinner; or a mild chalybeate water for tonic purposes may be ordered for the later doses. It is usual for short walks to be taken between successive glasses of water, and beautifully laid out gardens and walks are an important part of the armamentarium of the spas.

Modifications of the water may be made under certain conditions. If hot, it may with advantage be cooled, while on the other hand, the heating of some of the cold mineral waters increases digestibility and absorption. The heating of radio-active, gaseous waters, however, materially alters their composition, and they should always be drunk in a fresh state at the spring, if their specific action is required at its maximum. In the milder waters, which have little or no aperient action, purgative salines are often added, while in other cases, a useful modification is obtained by the addition of effervescent alkaline compounds.

A complete list of mineral waters occurring in Europe and India will be found in the appendix.

ELECTROTHERAPY

General considerations. Any form of physical energy applied to the body will produce first a physical effect, and this in turn will be transformed into some form of physiological activity. It may serve to stimulate function, promote metabolism or relieve pain. If applied beyond the degree of physiological toleration, destruction of tissues will occur. The primary physical effects of electrical energies applied to the body are either thermal, electro-chemical or kinetic. The clinical use of thermal effects by high frequency currents in the form of medical and surgical diathermy has been in the foreground of medical

interest during recent years. Galvanic and faradic currents in different forms have also a wide field of utility.

Galvanic current. When applied to the human body through suitable electrodes, the galvanic current produces primary physico-chemical effects (1) at the point of contact of electrodes (polar effect), an acid reaction at the positive pole and an alkaline reaction at the negative pole. There is also (2) a change in the electro-chemical concentration of the tissue fluids in the path of the current (inter-polar effects). The physiologic sequence of the chemical changes produced by the galvanic current is tingling and pricking under each electrode and a feeling of gentle warmth in the area treated. After a treatment, when the electrodes are lifted off, there will be a visible hyperæmia of the skin corresponding exactly with the area covered by each electrode; this represents the dilatation of capillaries of the skin produced by the mild chemical stimulation of the current. This 'counter-irritation' is accompanied by increased local circulation and nutrition of the parts between the electrodes. This improvement in the circulation and consequent relaxation of the tension of the tissues is probably responsible for the relief of pain by galvanic current.

Faradic or static current. The static current is peculiar in that it is of high voltage and of extremely low milliamperage. The current is specially useful as it produces a pronounced decongestion in tissue. It is used in the treatment of neurasthenia, general or nervous debility or neuralgia. It is of use also in acute myositis and in the absorption of inflammatory exudates from the joint. The galvanic and faradic currents are employed, both generally and locally for their stimulating action.

Locally, the galvanic and faradic currents find their chief employment in cases of muscular paralysis, both to prevent degeneration or atrophy, when nervous control has been lost, and to build up healthy muscular substance when atrophy has occurred from disuse. The *sinusoidal current* is perhaps the most useful to employ in the earlier stages; in this the current is continuous, but is made to vary in strength in a smooth and wave-like fashion without sudden interruptions. Later, the interrupted galvanic current is more useful, and is often the only one to which response can be obtained, whether before operation or in the earlier stages of repair. The current must be made and broken at regular intervals, a metronome introduced into the circuit being a useful contrivance. Failing this, the patient may be instructed to remove and replace one of the terminals at regular intervals, thereby stimulating his interest in his own case. When once a response is obtained to the faradic current after an operation for nerve-suture, this type of electricity should be substituted for the galvanic current as being more effective.

In therapeutics, electricity is employed in various ways :—

(1) **Electric bath.** In this patient lies in water to which a small addition of salt is made, and through which a galvanic current is passed. The effect of this is to increase the superficial circulation and produce cutaneous hyperæmia. It is often useful in diffuse rheumatic and gouty fibrositis, as also in conditions in which the general muscular and nervous tone of the body has been lowered. It is of considerable value in the treatment of conditions depending on arterial spasm, such as Raynaud's disease, and also to prevent chilblains in paralysed limbs. Care must be taken only to increase or decrease the strength of the current gradually, otherwise the patient may experience an unpleasant shock.

(2) **Electrolysis.** This is used chiefly for the destruction of superfluous hairs, moles, etc., and the treatment of nævi, where excision is undesirable. The passage of a current of sufficient strength, between metallic poles actually inserted into the tissues sets up an electrolytic action, and coagulation of the blood or local destruction of hair follicles results. Organisation of the thrombus leads to obliteration of the vascular spaces and the disappearance of the tumour. The clot formation is most marked at the positive pole ; hence it is often unnecessary actually to insert the negative needle into the tissues, but to use an ordinary flat pad moistened with salt solution and applied to the skin away from the part to be treated. At the negative pole a caustic alkaline compound is formed which may lead to sloughing of the tissues and scarring.

(3) **Ionization or ionic medication.** Ionization, ionic medication or cataphoresis consists in the introduction of chemical substances or drugs directly into the living tissues of the body by means of an electric current. Other terms like 'iontophoresis' or 'percutaneous' electro-osmosis' have also been used in different countries to describe the same form of medication. It is interesting to note that ionisation is not a new development in therapy, as is generally believed, but was enunciated as early as 1747. Palaprat claimed to have introduced iodine into the tissues in this way in 1833, and there are numerous references in the literature from that time onwards. During recent years, interest in this subject has been revived by the work of Professor Ledue of France.

Principle of therapy. In solutions containing acids, bases and salts, the molecules of these divide into positively and negatively charged ions even without the flow of any current. When a galvanic or direct current passes through such a solution, it causes a migration of the ions, in accordance with the polarity of the current. Ions with a positive charge—zinc, copper, quinine, cocaine are repelled by the positive pole ; those with a negative charge, like iodine, chlorine, salicylic acid, are repelled by the negative pole.

If the human body is interposed in the circuit instead of a solution of a salt in a vessel, and pads soaked in a solution of a salt or drug, are placed between the skin and the electrodes, kations at the positive pole and anions at the negative pole will enter the tissues and be disseminated in them. Prof. Ledue's classical experiments of producing strychnine poisoning in rabbits by driving it into the tissues by an electric current proved that drugs do penetrate the tissues by this method. Modern clinical and experimental evidence has, however, shown that ionic medication is of specific value only in pathologic changes of the most superficial tissues, as ions entering the body, are deprived almost immediately of their charge by the electrolyte salts of the body fluids, the blood-stream and lymph. The much-heralded beneficial effect of ionization on arthritis, etc., was found to be attributable to the passage of the galvanic current itself and not to any ionic medication, and the difference in reaction of the skin was shown to be due to difference in counter-irritation by the specific drug.

Depth of penetration of ions. The depth of penetration of the ions such as zinc, copper, silver, may be estimated with the naked eye, the depth of staining being an accurate indication. Zinc usually shows a white colour about the needle and in the softer subdermal tissue, the extension will be noticed over a large area. In granulation tissue, a still greater penetration is noticeable. The degree of diffusion depends upon the strength and duration of the current, which must depend upon the toleration of the patient. Ordinarily a current of 3 to 4 milli-amperes per square centimetre of the surface, maintained for 10 to 15 minutes, can be tolerated without any inconvenience by patients. In certain cases, stronger currents are required to drive the ions into the tissues. Under these circumstances, anaesthetics have to be used to numb the parts before the process of ionization starts.

Drugs used for ionization. Ionization has been carried out with a large number of drugs. Zinc, copper and silver ions have been most frequently utilised. Heavy metals like mercury, magnesium and lead have been successfully driven into the tissues. Potassium ferricyanide, ferrous sulphate, arsenious acid, iodides, etc., have also been used from time to time. Quinine, cocaine and adrenalin are less frequently used.

The solutions of the drugs employed for ionization should be well diluted, otherwise dissociation of the ions does not take place readily. One to two per cent. solutions are usually employed by most workers, but this has to be varied, using the tolerance of the patients as a guide. Compound solutions of iodine have been diluted from 5 to 20 times according to the sensitivity of the skin or the mucous surfaces.

Therapeutic possibilities. Ionization with different chemicals and drugs has been employed in chronic arthritis, sciatica, lumbago, etc., with success. In the treatment of sinuses, chronic ulcers, rodent

ulcers, lupus, warts, and neuritis, potassium iodide and sodium salicylate have been used and the reports certainly indicate that the method deserves further trial. Copper ionization is used to make sluggish wounds such as varicose ulcers to heal. It is also useful in chronic endocervicitis, a strong current of 10 to 12 milliampères being used for 20 minutes. Zinc ionization is useful in chronic otitis media, intermittent nasal obstruction, ethmoiditis, oriental sores, etc., but the benefit is often temporary. Chlorine ionization serves to loosen superficial scars. Dense superficial scars, if not too extensive, are made pliable and thus readily amenable to subsequent mechanical stretching by massage and other means.

In dermatology, ionic medication has got many supporters and this form of therapy is practised to a fairly large extent. Shaffer has used iodine solution in coccigenic sycosis, dermatitis, papillaris capiti, lupus erythematosus, pruritus ani and verruca. Arsenious acid has been used by others in psoriasis and copper ferricyanide for ringworms. In skin actinomycosis, iodine solution has also been employed by ionization.

(4) **Diathermy.** The term diathermy or 'heating through' means the passage of a special kind of current through the body. During the passage, heat is generated in all parts traversed by the current, so that the tissues are heated directly, simultaneously and throughout. Many terms have been used by other workers, in place of diathermy, such as 'thermo-penetration,' 'transthermy' and 'endothermy,' but the first one is now established and most widely used. When other methods of heating are employed, the heat never penetrates beyond a certain distance from the skin, *i.e.*, epithermy is produced.

In order to produce diathermy, an electric current which alternates at an exceedingly rapid rate is used. Such currents are commonly known as 'high frequency' currents. Its main characteristic is that it does not stimulate the excitable tissue nor cause any chemical (electrolytic) changes and, therefore, it can be raised to a strength sufficient to generate perceptible heat. In order to do this the current must reverse at a certain rate per second which depends on its strength; the stronger the current, the higher should be the frequency of oscillation. But there is a critical height, beyond which the current loses its stimulating and electrolytic powers, whatever the strength may be. The height of its frequency of oscillation cannot be definitely stated but it may be regarded as not less than 500,000 per second.

The diathermy current does not distribute itself like the constant current. Its path and distribution depend on the resistance of the conductor, its capacity, the self-induction that takes place in the conductor and the frequency of oscillation. The position of the electrodes is also very important

Medical diathermy. By it is meant the use of the high frequency oscillatory current, to produce heating through the body in disease. It may be local or general.

Surgical diathermy. The term has been used by English authors to denote the use of the high-frequency current for heating abnormal tissue to a degree high enough to coagulate or boil the fluid within it. But this is only one amongst the various uses of the high-frequency current in surgery at the present day. The term surgical diathermy is not a comprehensive term and it is better to include all the methods under the heading 'Electrothermic methods of surgery.' These methods are employed to destroy and remove new growths, both innocent and malignant, and infective granulomata. The main advantage is that the effects are obtained without disturbing anatomical continuity. There is no risk of hæmorrhage or of artificial metastasis and dissemination of infection.

Therapeutic uses of diathermy. The therapeutic effects are those of heat. It is, therefore, valuable in the relief of congestion and chronic inflammation where it acts by inducing hyperæmia and acceleration of blood and lymph-flow through the affected part.

Pain due to congestion or neuritis, is often relieved by diathermy and it is much more effective than surface heating. Pain associated with muscular spasm is also relieved by diathermy, as in cases of fissure of the anus and hæmorrhoids.

In cases of dysmenorrhœa of the painful contraction or congestion type, diathermy is very useful and its application to the interior of the pelvis for a few days before the onset of the menstruation often renders the period painless.

Cases of high blood pressure are effectively treated by diathermy. It lowers the blood pressure and alleviates the accompanying symptoms. Very likely the heat produced lessens the viscosity of the blood and thereby lowers the peripheral resistance. It also lessens the tone of the arterioles. The heart is thereby relieved of some of its work. It is also useful in the following cases: (1) Diseases of the urogenital organs in women, *e.g.*, gonococcal urethritis and endocervicitis, infective endometritis, salpingitis, erosion of cervix, parametritis and perimetritis. (2) Diseases of urogenital organs in man, *e.g.*, gonococcal prostatitis, and vesiculitis, gonococcal epididymitis and orchitis, urethritis. (3) Diseases of joints, bones and fibrous tissues, *e.g.*, arthritis or osteoarthritis. (4) Diseases of the nervous system, *e.g.*, peripheral neuritis, paralysis agitans, anterior poliomyelitis, neuralgia associated with herpes zoster, trigeminal neuralgia, metatarsalgia, coccydynia, fibrositis, angina pectoris, intermittent claudication, Raynaud's disease, chilblain, acrocyanosis, have been treated with good results.

Diathermy should not be applied to regions from which hæmorrhage has occurred or is likely to occur. Some authorities are of the

opinion that diathermy is inadvisable in acute infections and recent injury. It should not be applied during menstruation, there is a risk of increasing the loss of blood. Anaesthesia of the skin is a contra-indication. Due to the loss of power of perceiving heat the patient may fail to give information when the degree of heating is definitely damaging to the tissue.

Methods of application. These are:—(1) Local diathermy. (2) General diathermy. (3) Labile method of diathermy, *i.e.*, by moving the active electrode over the region to which diathermy is being applied. (4) Combination of diathermy and massage.

Dosage. In the present state of our knowledge it is difficult to lay down any precise rule. For the production of sedative effects weak current should be used in the earlier stages of infection or injury and the duration should be relatively long. As the case progresses the degree of diathermy may be increased and its duration shortened. In all cases where there is any doubt it is always safe to commence with a small degree and apply treatment for a longer time. The temperature of the skin or mucous membrane and the time for which the rise of temperature is produced are the only accurate measures of dosage.

RADIATIONS IN THERAPY

Radiation means the transference of energy by means of vibrations propagated in the ether at a velocity of 3×10^{10} cm. per second. The electro-magnetic theory of Faraday and Maxwell regards these vibrations as oscillatory changes of the electric charge and magnetic induction. Modern sub-atomics requires that radiant energy should be propagated in empty space in discrete, undivided 'quanta' and that any atomic resonator must absorb a whole quantum or none.

The following is a resume of the position regarding the action of the various forms of radiation; taken from Clark's *Applied Pharmacology* 1933.

Electro-magnetic radiation. There are different forms of electro-magnetic vibrations, *viz.*, Hertzian waves, radiant heat waves, the rays of visible light, ultra-violet waves, X-rays and the gamma rays produced by radio-active substances. The property which differentiates one kind of electro-magnetic radiation from another, is that of wave length. Only those with short wave lengths have the property of producing some physiological effect on the living tissue, and the shorter the wave length, the more marked is the effect produced. Radiant heat has been employed in therapeutics to produce local vaso-dilatation, while the visible light rays stimulate the retina. It is only those vibrations whose wave

lengths are shorter than those of the visible light rays are of importance in their therapeutic action.

The electro-magnetic waves form a continuous series between two extremes of wave length, *viz.*, 30 kilometers (Hertzian wave used in wireless telegraphy) and 10^{-10} cm. (gamma rays). But there is a marked difference between the power of penetration of light waves and X-rays. The passage of light waves through a media depends upon the arrangement of the atoms in a molecule, whereas that of the X-rays or gamma rays is solely determined by the nature of the atoms. In other words, the light waves are stopped by molecules, and X-rays and gamma rays, by atoms. On account of this curious behaviour, the relation between wave length and the ease of absorption is rather peculiar. The shorter the wave length of the light waves, the lesser is their penetrative power, while on the other hand, the shorter the wave length of the X-rays and gamma rays, the greater is their penetrative power.

Light sensitisation. There are certain substances in nature, which act as photo-sensitisers and which have the remarkable property of sensitizing the body in such a manner that the ordinary visible light rays produce the same effect as the ultra-violet radiations. For instance, paramocia are not affected by acridine dyes in the dark, but are readily killed when exposed to light. Hæmatoporphyrin acts in a similar manner and it has been shown that exposure to light subsequent to injections of hæmatoporphyrin produced an intense oedema of hands and face. Smallpox, pellagra and certain other diseases associated with excretion of porphyrin produce sensitisation of the skin to light and much of the damage that is done to the skin, can be averted if the patient is completely protected from all actinic rays.

Ultra-violet lights. For all practical purposes the ultra-violet radiations are divided into the near ultra-violet radiation (wave length between 3,900 A.U. and 3000 A.U.) and the far ultra-violet radiations (wave length less than 3,000 A.U.). The near ultra-violet radiations are not of much physiological importance, those lying between 3,000 A.U. and 2,800 A.U. have some therapeutic value. They produce in man, tanning of the skin and also activates ergosterol in the skin, and thus produce anti-rachitic vitamin. The direct action of ultra-violet radiation on man is due entirely to their action on the skin and the blood passing through the skin. Over-exposure to the ultra-violet radiation causes severe burn in the skin and inflammation of the conjunctiva. The effect usually appears some hours after the exposure. Ultra-violet light also causes contraction of plain muscles and exerts a bactericidal action on the micro-organisms.

It produces histamine in tissues, and this may explain the burns produced in the skin and contraction in plain muscle. Excessive exposure to ultra-violet radiation insufficient to produce burns, may produce general toxic reaction. Some of the symptoms produced are headache, malaise, tachycardia, rise of temperature, and insomnia.

The available source of this energy, in nature, is entirely traceable to sun light. Sun light contains ultra-violet rays extending from 290μ to 380μ approximately from 380μ to 780μ of visible light and from 0.78μ to 3.0μ of infra-red rays of fairly high intensity. But most of the ultra-violet rays from the Sun are absorbed in the atmosphere and the pollution above the towns absorbs a large proportion of both the visible and ultra-violet rays. Through clear air, ultra-violet rays down to 2,970 A.U. penetrate during summer and down to 3,060 A.U. during the winter. The chief artificial sources of ultra-violet radiation are mercury vapour arc-lamps enclosed in quartz, and carbon arc-lamps either bare or shielded with quartz. These artificial sources produce the radiations of far greater intensity than sun light and therefore, great care need be exercised in their application.

Ultra-violet radiations, whether obtained from nature or from artificial source, are powerful therapeutic agents. Our knowledge regarding their action is very imperfect. The limit of the wave lengths that produce beneficial effect is not well known, but probably it lies between the wave lengths of 3,500 A. U. and 2,800 A. U. The therapeutic properties are in the main limited to conditions of growth or of functions that are below normal. For example, it has been found to increase body weight to increase the rate of growth, to improve the mineral content of blood, to increase the functional activity of the endocrine glands, to increase the bactericidal power of blood, etc., where these are below normal. Rollier in 1903 commenced the treatment of tuberculosis other than the pulmonary type. His method commences with the exposure of the feet to the Sun for a few minutes each day, gradually increasing both the time and the area exposed until finally the whole body of the patient is exposed to the Sun for several hours daily. Perhaps it is true that at the present time the best guide to dosage is the degree of erythema which results after a test exposure, since most other methods take no account of the idiosyncrasy of the patient.

The experience goes to show that non-pulmonary tuberculosis rickets, malnutrition, and certain skin diseases respond well to treatment. Two mechanisms, which have a chemical bearing, have been suggested for curative process—(a) the photosynthesis of vitamin D and, (b) an increase in the bactericidal power of the blood. As a working hypothesis it may be assumed that ultra-violet irradiation helps to regulate calcium-phosphorus metabolism by means of the forma-

tion of vitamin D and at the same time increases the resistance of the blood to noxious bacteria. The evidence available at present is so contradictory and the matter is so obscured by controversy that it is impossible to form any definite estimate as regards the action of ultra-violet therapy on general health and disease.

X-rays. Whenever rapidly moving electrons hit matter x-radiation is generated. The exact nature of x-rays still remains in doubt. Whether the x-rays have a chemical or electrical or mechanical influence on animal tissue, is not yet fully understood. The effect produced by x-rays depends on three primary facts: (1) the intensity of the rays, (2) the duration of exposure and, (3) the wave length of the rays. The changes produced vary within wide limits with the susceptibility of various groups of cells. The group of cells most sensitive to x-rays, are the lymphatic tissue, and glands, the leucocytes, ovaries, testes, the suprarenal and various other glands with internal secretion, like the thyroid, the thymus, spleen, etc. Considerably less sensitive are the skin, the mucous membrane, the hair follicles, the kidneys, etc. The cells of the muscles and bones are the least sensitive. It is supposed that those cells, which are near the stage of sub-division, are the most vulnerable.

Reactions and dangers. X-rays in sufficient dosage produce slight temporary erythema and a temporary falling off of the hair. The changes produced by x-ray exposure do not become noticeable immediately after, but microscopic and chemical analysis may reveal changes within half an hour after exposure. When the tissue has been exposed to moderate doses, which will cause erythema to appear a week after, a faint redness and a slight itching or a burning sensation are noticed within a short time. With doses of sufficient strength, the irritation becomes so violent that even organs like skin, become atrophied and shrink or when exposure is excessive, ulcers and abscesses form. The administration of x-rays over large areas of the body sometimes produces a general reaction. The x-ray sickness forms a definite syndrome characterised by headache, loss of appetite and, in more severe cases, vomiting and diarrhoea. These toxic effects are readily induced after irradiation of the

abdomen and especially of the liver region. They are probably due to the injurious action of the x-rays on the mucosa of the alimentary tract and on the liver. The effects may possibly be intensified by ozone and other gases produced by the spark and discharge.

Units of x-ray dosage. The accepted unit for biological effect is that dose which will produce erythema of the skin and this is known as the unit skin dose (U.S.D.). The erythema dose as a unit is rather inconvenient, because it takes some time before the results show. It is also insufficient, because it shows only the intensity of the rays which prevailed on the skin, but does not indicate the intensity of the rays which penetrated to objects 6 to 10 c. cm. below the skin. It is, therefore, necessary to employ electrical or chemical quantimeters which enable us to determine the dose during the exposure on the skin, or at various depths below it. There are various chrono-radiometers which measure the colour change produced in chemicals by x-rays. The duration of the exposure which is necessary to produce a U. S. D. depends on many factors. The most important are the voltage, milliamperage, focus skin distance and filter. It is also influenced by the type of apparatus which is used. The actual time for the U. S. D. must be found experimentally for each apparatus.

Therapeutic application. X-rays are now the therapy of choice in many diseases of the skin. They are of importance in ear, nose and throat diseases, in exophthalmic goitre, and in the treatment of tumours in brain. In blood affections, such as leukæmia, in neuritis, in neuralgia, and in cases of arthritic joints they are applied with some success. The biggest field, however, is in gynecology. In the treatment of excessive hæmorrhage due to approaching climacterium or to fibroids or myomata, cure is achieved by exposure to x-rays lasting not more than $1\frac{1}{2}$ to 2 hours altogether. The cells of malignant disease may be killed or at least paralysed by doses of x-rays, but their value in the treatment of carcinoma is still doubted. The depilatory action of unfiltered x-rays is utilised in the treatment of ring worm of the scalp and occasionally in sycosis. X-rays are also used to reduce the sweat secretion in hyperhidrosis and to destroy both benign and malignant tumour of the skin. When the part of the body to be treated is situated below the skin, the application of x-rays is termed deep therapy. There are two types of deep therapy—medium deep therapy and deep therapy.

X-rays for medium therapy are not used as a destructive agent but are employed to set up certain biological changes or only a partial destruction of cells. In the case of deep therapy x-rays act as a destructive agent and are employed in localised conditions in deep-seated organs, carcinoma of the uterus, cervix, etc. To obtain the desired effect the cells of the growth should be actually destroyed. The doses should, therefore, be larger and the radiation should be penetrating that it may arrive at its goal in sufficient intensity without being heavily absorbed before it gets there.

X-ray diagnosis. The application of x-ray photography to diagnosis depends on the relative opacity of bone and flesh to the passage of the rays. The use of bismuth salts as an opaque lining for showing up the alimentary canal, of red lead for rubbing the finger tips for recording the design for finger prints are interesting side lines. The x-rays are readily arrested by atoms of high atomic weight, and suspension or solution of inert substances containing atoms of high atomic weights are introduced into certain body cavities and x-ray photographs are taken. Barium sulphate and bismuth salts are used as test meals for the study of the alimentary tract. Sodium tetra-iodophenolphthalein is used to render the gall bladder and biliary tract opaque and iodised fats or oils are injected intrathecally to permit photograph of the intrathecal space. Certain complex iodine compounds (Uroselectan B), which are readily excreted by the kidneys, are used radioscopy of the urinary system.

RADIO-THERAPY

In recent years radium has come to be used extensively in medicine. The fascinating history of the use of radium dates back as early as the times of the Romans. Some of the Roman spas were credited with the power of containing mystic cures. In the United States of America, the spring water of Saragota was said to have the power of curing various ailments. In Europe the district of St. Joachimstal earned a reputation owing to the healing power of its earth. People from different parts used to flock to the place to take the water, or to breathe the air in the mountain groves. Later, in the eighteenth century, attention was diverted to some Austrian springs. The wonderful healing property of the water of these springs was ascribed to electrical effects. In 1835 Burckhardt

Eble stated that this water contained a gas which was later proved to be nothing but radium emanation.

In 1896, Mme. Curie working in her laboratory in Paris, discovered radium and separated it from St. Joachimstal ore and since then the so-called mystic 'cures' that were ascribed to many spring waters and ores, were definitely known to be due to the presence of radium, which has now secured a lasting place in the realm of scientific medicine.

Nature of radio-activity. A radio-active substance has been defined as a substance which possesses "the property of emitting spontaneously radiation capable of passing through sheets of metal and other substances opaque to light and having the power of imparting electrical conductivity to the air." Radium is the most important member of the radio-active substances. It is a bivalent element closely related to barium. Radium is marketed in the form of soluble bromide or dichloride, because in the metallic state it undergoes rapid chemical alteration. Radium and other radio-active substances owe their radio-active property to spontaneous disruption into simpler atomic bodies and emitting certain emanations during this process of decay. These emanations are accompanied by the generation of rays which produce destructive or irritating effects.

The decomposition is spontaneous and goes on steadily at the same rate, the temperature and chemical composition being changed without producing the slightest visible effect. Other radio-active substances are thorium, uranium, ionium, solonium.

Disintegration of radium. Radium is constantly undergoing atomic decay and during the disintegration it produces three types of rays—the alpha, beta and gamma rays. This breaking up process is going on at a slow rate; roughly one atom in every hundred thousand million atoms blows up in one second. If we start with a certain number of atoms of radium, they will gradually become less and less. As the quantity of a given radio-active substance gets less, the actual number of atoms decomposing per second will also be fewer. It has been estimated that a radio-active substance will fall to half its original value in about 1,690 years. The first substance produced by this gradual decay is a gas called *radon*; it does not enter into chemical combination but is radio-active and decomposes in its turn, the time to decay to half-value being 3.86 days. From radon a whole series of radio-active substances

originate, mostly of short life, with successive losses of alpha, beta and gamma rays. These are radium A, B, C, D, E and F, the most penetrating rays being given off by the C group.

Varieties of rays—Alpha rays. In the decomposition of radium a fragment of the original atom is projected at a high speed carrying a positively charged helium atom. This is what is known as an alpha ray. The alpha particle is a bulky body and is rapidly stopped when it comes into collision with air or any surrounding structure. A screen or tissue-paper or a layer of varnish can cut off all the alpha rays, and in actual radium therapy needles are made of platinum so as to cut off all the alpha rays. The maximum distance through which the alpha rays can travel is 0.09 mm.

Beta rays. These are electrons, carrying negative charges of electricity. The beta rays are more penetrating than the alpha rays owing to the small size of the particle, the maximum speed through soft tissue being 2 cm. They can penetrate through several thicknesses of paper or thin sheets of metal or glass; most of them are, however, stopped by 2 mm. of aluminium, 1 mm. of lead or 5 mm. of muscular tissue.

Gamma rays. These are true radiations. They are electro-magnetic vibrations in ether and are similar to x-rays but of shorter wave length and greater penetrating power. About 62 mm. of aluminium is necessary to reduce the rays to one half, and about 50 per cent. are absorbed by 7.6 mm. of muscle.

During the process of decomposition of radium all the three types of emanations are not produced at the same time, but if contained in a sealed tube, the radium soon arrives at an equilibrium so that the decomposition products are uniform as happens when the metal is contained in platinum needles. When radium exists in a natural state, the gas radon is being constantly given off. In the formation of natural spas containing radio-active substances, water percolating through radium-bearing strata comes in contact with this gas radon which is thereby carried away in solution, and to this the curative property of the water is due. But as radon is constantly decaying it is very likely that most of the spring waters lose their radio-activity on keeping.

Units of radium. The common unit of radio-activity is the *curie*, that is, the amount of radon (radium emanation) which is in equilibrium with 1 gm. of radium. This unit being rather too large for practical purposes, the unit used is one-thousandth of this, that is, *one millicurie*, which corresponds to the emanation of a mgm. of radium; the emanation from 0.001 mgm. corresponds to a *microcurie*. 'Mache' unit is approximately $1/2,700$ of a microcurie, but this standard has now been discarded.

Pharmaceutical action. The action of radium and radio-active metals is due to the three varieties of rays that they emanate. The softer alpha rays are less penetrating than the hard beta and gamma rays, but they have more intense local action. On protozoa, the alpha rays produce a

rapid lethal effect; the beta and gamma rays have a marked effect upon the developing cells and cells in active state of division; sublethal doses of the latter stimulate all forms of growth.

The action of radium emanations on the skin resembles that of the x-rays. They produce dermatitis after repeated exposure. The alpha rays, which are more superficial, produce more marked effect. This consists of rubefaction and pigmentation of the affected area which pass on to vesication and loss of hair after several days. The blisters may rupture exposing a raw area progressing ultimately to indolent ulceration; when the corium is destroyed the ulcer is deep-seated and the epithelium of the skin invades the underlying tissues producing malignant changes.

The effect on the nervous system is quite characteristic. Mice exposed to large amounts of radium emanations show the following train of symptoms:—forced movements, convulsions, paralysis of extremities, ataxia, paralysis of sphincter control and trophic disturbances. Autopsy shows intense congestion of the spinal cord and brain and degenerative changes in the nerve cells. In man, over-exposure has produced general weakness, vomiting, coma and asthenia and even death.

The germ cells in the ovary and the testis are rapidly destroyed by exposure to radium. *In vitro* the spermatozoa of guinea pig lose their motility, the ovum is also affected; but the interstitial cells remain unaffected. Continued exposure in women may lead to the atrophy of the ovary and menopause.

The gamma rays have a profound effect on the lymphoid tissues; the spleen, lymphatic glands, thymus and Peyer's patches in the intestine show atrophic changes after exposure. Brill and Zehner (1912) found that repeated injections of radium salts increased the number of red cells, this effect persisting for several weeks. The rise in hæmoglobin percentage was not marked. The leucocytes were increased with small doses but diminished by large doses. The following table from Helber and Linser (1905) shows the effect of exposure of rabbit's blood to x-rays.

			Before exposure	After exposure
Red blood cells	7,00,000 per c.mm.	4,50,000 per c.mm
Hæmoglobin	80 per cent.	55 per cent.
Leucocytes	6,500 per c.mm.	1,400 per c.mm
Lymphocytes	2,000 per c.mm.	84 per c.mm
Polymorphonuclears	4,000 per c.mm.	500 per c.mm

The coagulability of the blood is said to be markedly increased, *in vitro* the red corpuscles of the guinea pig and sheep are hæmolyse. The capillaries and the endothelium of the blood vessels seem to be specially liable to injury; after irradiation, skin vessels are dilated, there is

diapedesis of leucocytes and later, swelling and extravasation occurs; the blood pressure is said to be lowered.

Fate of radium in therapeutic doses. When soluble radium salts are taken by the mouth or given by injection they are absorbed rapidly, permeate through the tissues freely and are stored in the liver and spleen. Excretion proceeds slowly and occurs mainly by the intestines and some portion by the urine; when given in the form of emanations some breaks up into its degradation product radon and into alpha rays. Radon can be detected in the expired air.

Method of Administration of Radium

Radium emanations. Radium emanation is a gas, given off by the disintegration of the metal. This gas *radon* is being constantly given off from the radium-bearing strata in the earth due to which many natural waters exhibit healing power. In order to obtain the benefit of radio-active waters, away from their source, an apparatus has been devised. It consists of a metal cylinder with a bucket containing the radium salt; this is surrounded by water and left for 24 hours by which time it becomes radio-active. For breathing radio-active gas, air is bubbled through a solution of radium salt; such air gets charged with radon which can then be inhaled.

Radium packs. Radium in packs and pads has been used for a long time in the treatment of rheumatism and similar disorders. They consist of compresses of radio-active substances, sewn in a bag of water-proof material which in its turn is contained in a loose washable cover. These compresses are applied moist and warm to the affected part and left in position for several days.

By mouth. Radium salts, such as radium chloride can be safely given by the mouth in dose of 1/100,000 mgm. several times a day for a number of weeks at a time.

Radium in platinum tubes. Radium when contained in platinum tubes, emits all the three types of rays but platinum cuts off the softer rays allowing only the gamma rays to pass through. This is particularly useful in treating tumours.

The alpha rays have a more intense local action while the beta and gamma rays have less; the gamma rays are specially employed in deep tissues such as tumours. When the action on the skin is desired, as in the treatment of skin diseases, flat applicators are used on which is spread a thin film of salts of radium by which only the alpha rays are allowed to act on the surface of the skin. For purposes of deep therapy it is necessary to cut off the more intense alpha rays, and for this, the rays are filtered by allowing them to pass through some screen of metal. Radium is enclosed in a tube of aluminium, silver or platinum; by this method only the hardest rays are allowed to emanate, the local action is reduced and the rays that

emanate have more lasting and penetrating action on the deeper structures. Aluminium filters are used when treating superficial lesions; silver filters are used for burying tubes and have stronger local action; platinum is employed in the form of tiny needles and embedded in deep structures like rapidly growing tumours. Lead filters have the power of excluding both alpha and beta radiations. The following table from Clark gives the effects of filters on beta and gamma rays from radium.

	Per cent. β -rays transmitted	Per cent. γ -rays transmitted
Lead, 2 mm. ...	0.37	92.8
Platinum, 0.3 mm. ...	2.28	97.2
Silver, 1.0 mm. ...	1.18	95.5
Aluminium, 0.2 mm. ...	63.2	99.8

Therapeutic uses.—Radium is employed in medicine in two ways:—‘Mild radium therapy’ or ‘deep radium therapy.’ Mild radium therapy is intended to mean administration of radium salts in minute doses, or to administer the radium emanations in amounts corresponding to quantities found in natural waters or the external application of radium by means of packs and pads; ‘deep radium therapy’ signifies the treatment of growths and morbid conditions by prolonged exposure to radium.

Mild radium therapy.—Various painful conditions are amenable to mild radium therapy; among these may be classed gout, rheumatism, lumbago, sciatica, varicose veins, neuritis. Even trigeminal neuralgia is said to be favourably influenced by it. Nathan Mutch (1931) states that radium chloride in doses of 1/100,000 mgm. several times a day produces a beneficial effect in arthritis. There may be initial inflammatory reaction, but at the completion of a short course it subsides and is usually followed by beneficial effects; similar results are obtained by the administration of a solution of radon or emanation in water. Mutch (1931) treated series of cases of high blood pressure with small doses of radium. He showed that such doses have a beneficial effect on high blood pressure uncomplicated by kidney disease; in his series of cases pressure reduction varied from 12 to 54 mm. of mercury. Good results have also been reported in angio-neurotic cedema. Leukaemia is treated by exposure to radium or by X-rays. There may be a

temporary decrease in the leucocyte count and also clinical improvement, but the effects are not all permanent. It is generally applied over the spleen or on the bones.

Mild radium therapy is also useful in certain dermatological conditions. The physiological action of mild radium therapy is a stimulation of cell activity arousing all secretory and excretory organs and favouring the elimination of all toxic materials. At the same time the stimulation of the cell activity promotes all metabolism and raises the vitality of the tissues. This explains the beneficial effects of many spas. "Large numbers of people visit the spas for such cures. The radio activity in such cases is due to the presence of radon in the water itself and the gas which accompanies the flow of water from the springs. Accordingly Von Noorden and Falta, in contradistinction to all other forms of electrotherapy, the radio-active substances possess a means of carrying electrical energy into the depths of the body and there subjecting the juices, protoplasm and nuclei of the cells to an immediate bombardment by explosions of electrical atoms. The internal treatment with radioactive waters may, therefore, be designated as internal electrotherapy. In some spas there is also provision for inhaling naturally occurring emanations and this is done by placing the patient in a compartment where such radio active water is flowing.

Intensive radium therapy. Intensive radium therapy has its special field of application in the treatment of new growths. The susceptibility of tissues to radium is dependent on the rate of growth; the rapidly proliferating tissues such as tumours are more susceptible than normal tissues. Malignant tumours are more easily destroyed than benign ones, sarcoma being more susceptible than carcinoma or lymphoid tissues; the ovaries and the testicles and the endothelium of the capillaries are especially susceptible. Nerve and muscle cells are not very sensitive.

The radiosensitivity of a tumour is dependent upon cell structures and the biologic qualities of the parent tissue. Location of a tumour in bone or fat tissue renders it radio-resistant. Active infection interferes with successful irradiation. Successive treatment with inadequate dosage makes the tumour

resistant to radiation. Likewise a tumour becomes radium-fast after a series of treatment with high dosage. Introduction of certain salts (cerium-iodine) into tumour may artificially increase radiosensitivity. Biologic sensibilization has also been practised in some cases; pituitary gland irradiation exerts a beneficial effect in malignant conditions of the female genital tract.

The use of radium in the treatment of tumours is comparatively of recent origin. Special skill and technique are required to decide whether any particular tumour will be amenable to treatment and to select and apply the rays so that maximum therapeutic effects are obtained without any harm to the normal tissues.

For the treatment of superficial growths like rodent ulcers, radium is very effective. In cases of deep-seated tumours, radium may be applied by deep therapy or by implantation of tubes. The softer rays which have intense local action are filtered so that only the hard rays are allowed to pass through; in addition, radium can be applied to the growth from different angles so that any particular site of the tumour does not receive too large a dose.

The implantation of radium in the form of tubes to destroy malignant growths is now widely practised. The tubes are generally made of platinum or lead 1 to 2 mm. thick. These are imbedded in the growth; in general it may be said that 600 milligram-hour (one skin unit dose) destroys most malignant cells. This form of treatment proves effective in early stages; in advanced cases the results are usually discouraging. The most beneficial effects are seen in cancer of the cervix and tongue, cancer of the breast and rectum have also been treated with radium, but so far success has not been uniform.

Dangers of radium and x-rays. The reactions produced by irradiation in the treatment of arthritis are generally mild. These consist of local pain, redness and swelling; the temperature may rise and there may be depression, lassitude and insomnia. These subside in a few days without much trouble. The danger of artificially produced irradiated waters lies in over-dosage. Many preparations sold by quack vendors contain

dosage in excess of the therapeutic limit and this may produce harmful effects. In the treatment of malignant growths, the greatest difficulty lies in giving the proper dosage; sometimes the more actively proliferating cells may be stimulated by the action of radium leading to rapid metastatic changes.

Persons who work with radium show susceptibility to two types of injury with radium, the first due to local action and second the result of systemic absorption. On repeated exposures dermatitis develops which may go on to ulceration and even carcinomatous changes may occur. The rays have got a special destructive effect on the testis and the ovaries and sterility after prolonged exposure, is known. Decrease in the leucocyte count, and destruction of the red blood cells may also occur and in severe cases anæmia and cachexia develop.

Electrocution. With the rapidly increasing use of electricity in industry and for domestic use, electrocution has become quite common. The passage of a strong electric current or the lightning through the body kills the cells by producing electrolysis. The danger of a current passing through the body depends on the voltage of the current, the resistance of the body, and the direction the current takes. The passage of a current through the brain produces immediate unconsciousness. The ordinary alternating current, which alternates about 50 times per second, produces just as much effect as a direct current. Current that alternates very rapidly, *i.e.*, more than 10,000 times per second, is innocuous to the body.

The effects of lightning and high voltage electricity are most marked upon the central nervous system. They are, (a) focal petechial hæmorrhage scattered throughout the brain and especially the medulla. They may also be found in the spinal cord. (b) Chromatolysis of the pyramidal cells, the nerve cells of the medullary nuclei, and of the anterior horn and Purkinjee cells. (c) Curious wide dilatation of the perivascular space. (d) Localised ballooning of the myelin sheath of the peripheral nerves with fragmentation and tortuosity of the axons, breaking down of the sheath of Schwann and infiltration of the epineurium with endothelial cells. These changes do not depend primarily upon the strength of the current, but the duration of the contact and the length of the survival time determine the resultant features.

The main types of injury due to electricity and lightning are (1) *immediate*, including shock, unconsciousness and suspended animation, (2) *secondary*, including burns, gangrene and temporary nervous disorders and (3) *remote effects*, including neurological and ocular complications. The nerve tissues being poorly conductive, the nervous

CHAPTER VII

DIET AND DIETETICS IN THE TROPICS

The importance that the Indian patient attaches to his diet is not fully appreciated by Western practitioners. The Hakims and Kavirajes lay great stress on the subject of diet. In Susruta, the well-known book on Hindu medicine, it is said, "The physician that does not know the principles of dietetics cannot cure disease." This idea is ingrained in the minds of Indian patients and unless proper attention is paid to this aspect, patients are not convinced about the utility of a particular line of treatment. It is surprising, however, how few physicians practising Western medicine pay any special attention to this important subject. We have, therefore, thought it necessary to give a chapter on this important subject.

Food and its constituents. Food is essential for the maintenance of the body processes. The human body can be compared to a machine, the fuel for which is supplied by the food that we take every day. Food provides the materials for growth and repair of the fabric of the body. It supplies materials which can be oxidised in the body, with the result that the energy set free by oxidation may be used in performing work and in producing heat. It also supplies the body with substances (catalysts, food hormones, vitamins) which though present in almost inconceivably minute amounts, control body function. Food, therefore, is responsible for the conservation of the material of the body, the maintenance of its output of energy and for the regulation of its functions.

On chemical analysis, all foods resolve themselves into the following proximate principles usually known as the 'nutritive constituents.'

1. Proteins, *e.g.*, albumin, myosin, gluten, legumin, gelatin.
2. Carbohydrates, *e.g.*, sugar, starch, dextrin, glycogen, cellalose.
3. Fats, *e.g.*, suet, lard, olive oil, butter, fat.
4. Mineral matters, *e.g.*, common salts and compounds of calcium, iron, iodine, potassium, magnesium.

5. Extractives and flavouring materials.
6. Vitamins.
7. Water.

The various functions of food are fulfilled by the different groups in different measure. The first function, that of building up and repairing the tissues, can be fulfilled by the proteins, the mineral matter and the water. It is true, of course, that glucose, one of the carbohydrates, enters into the construction material of all nuclei, of the mucin of mucous cells and of cartilage; while substances like lecithin with a large portion of their molecules consisting of fatty acid derived from fat, appear in every cell in the body. These substances, however, are almost incidental to the structure of the body which in the main consists of protein, of mineral matter and of water. None of these is sufficient by itself. The second function, that of serving as a source of energy, is mainly fulfilled by the fats and carbohydrates, though we have to recognise that a fair proportion (10-15 per cent.) of the energy output of the body may be derived from the oxidation of the proteins. The third function, that of regulating the processes of the body, is fulfilled by mineral matter and by the vitamins. It is known that muscles (*c.g.*, heart muscle) will not contract in the absence of carefully adjusted amounts of mineral matter. Bone and teeth are irregularly and incompletely formed if in addition to the essential calcium and phosphorus in organic or inorganic combination, there be little or none of the calcifying vitamin, vitamin D, in the food. Many other of the processes of the body depend upon the supply in the food, of minute amounts of mineral matter and vitamins.

The relative value of foods. Physiological opinion has undergone considerable changes during the last century with regard to the relative values of proteins, carbohydrates and fats. Liebig thought that proteins were the chief producers of muscular energy while carbohydrates and fats merely acted as a fuel and maintained the body temperature. This view can no longer be maintained. It is largely a matter of indifference to the cells of the body whether they draw their supplies of

energy from protein, fat or carbohydrate although they can get it more readily from protein and carbohydrate than from fat. The maintenance of body temperature is a natural outcome of the metabolic activities of the cell and will be carried on as long as the cells are alive, irrespective of the nature of the food supplied. Tissue repair, however, is a much more important process than heat production and cannot be maintained without the presence in the food of protein, mineral matters and water. The proteins present should be complete proteins, *i.e.*, contain within them all the essential amino-acids; incomplete proteins such as gelatin cannot by themselves take the place of complete proteins in the diet.

The functions and the parts played by the different proximate principles can, therefore, be stated in tabular form as follows—(Hutchison and Mattram):—

Tissue formers and repairers.	Work and heat producers.	Regulators.
Complete proteins.		
Incomplete protein in the presence of complete proteins.	Complete and incomplete proteins.	Mineral matter.
Mineral matters.	Fats.	Vitamins.
Water.	Carbohydrates.	

It will be observed that the proteins appear in two categories out of three. They are thus of immense importance in the diet. A diet may be predominantly protein and yet life may be maintained thereon. Without protein, life is impossible as the daily wear and tear of tissue protein must be made good.

Determination of the merit of foodstuffs. From the point of view of physicians, a knowledge of the composition and the nutritive values of foodstuffs in common use is of prime importance, as without it, he will not be able to advise his patients as to the nature of the diet they should adopt. There are methods by which one can judge the relative merits of these food materials.

1. **Chemical analysis.** It can tell us how much protein, fat and carbohydrate are contained in hundred grammes of the

food and from this we can form an idea of the value of a particular food as a source of building material or energy.

2. **Physical test.** The amount of heat which a food yields on complete combustion may be taken as a measure of its value as a source of energy to the body. The unit of heat production is expressed in *calorie* which is the amount of heat required to raise the temperature of 1 gramme of water through 1°C . This is the small calorie. For convenience in measuring the amount of heat of foodstuffs, the large or kilo-calorie is used, i.e., the amount of heat required to raise 1 kilogramme (or 1 litre) of water 1°C . (or 1 pound of water 4°F). The determination of the caloric value of a food, therefore, gives an indication as to its value as a source of energy. The heat values of 1 gramme each ($15\frac{1}{2}$ grains) of protein, carbohydrate and fat are

Fat	...	9.3	Calories.
Carbohydrate	...	4.1	Calories.
Protein	...	4.1	Calories.

It will be seen that the caloric value of fat is nearly twice that of protein and carbohydrate. The caloric value of a food, therefore, is greatly affected by its fat content.

3. **Physiological test.** It is not enough that food should contain a considerable proportion of protein, carbohydrate and fat and should be capable of yielding energy on oxidation. It must be of such a nature that it is easily digested in the alimentary tract and absorbed more or less completely into the blood. There are many substances, *e.g.*, saw-dust, agar, hoof parings which are complete foods so far as their chemical analysis and physical properties of heat production are concerned but which nevertheless are not digestible and cannot serve any useful purpose to the body mechanism. In giving opinion on the qualities of a particular food, therefore, several factors have to be taken into consideration.

(i) *The digestibility of foods.* By digestibility, the biochemist means foods which are rapidly disintegrated in the body under the influence of ferments.

(ii) *The satiety value or satisfying power of foods.* This is a physiologico-psychological quality in which foods differ from one

another and is a property which cannot be properly explained. Several factors are at work in giving satiety value to a food and of these the duration of stay of a food in the stomach and the stimulation of the gastric juice are probably important. Fatty foods like milk, butter, eggs, etc., have a high satiety value while 'lean' fish, bread and green vegetables have a low one.

(iii) *Absorbability.* Absorbability of the different constituents of various foods is another important factor in dietetics. Of the three chief nutritive constituents, the proteins are the best and most completely absorbed. Animal proteins (milk, eggs, meat) are much better absorbed and the nitrogen loss is much less than in the case of the vegetable proteins (carrots, potatoes, peas, etc.). Compared with the proteins, fat is apparently very incompletely absorbed. This is probably due to the fact that a fat which is fluid at the body temperature is more easily absorbed into the blood than one which remains more or less solid. The carbohydrates are more completely absorbed than any other nutritive constituent of the food. Sugar probably never fails to enter the blood to the last grain and even starch only reappears in the faeces when taken in a form specially difficult of absorption, e.g., in green vegetables. Hence foods which consist mainly of carbohydrates, such as rice, leave on the whole, less solid residue in the intestine than any other.

A number of experiments have been made by the U.S. Dept. of Agriculture in order to ascertain the degree to which different constituents of various foods are absorbed into the blood. The results are shown in the following table:—

Kind of food	Protein per cent.	Carbohy- drates per cent.	Fat per cent.	Availability of energy per cent.
Meat and fish ...	97	—	95	87
Eggs ...	97	98	95	89
Dairy products ..	97	98	95	98
Total animal foods of mixed diet ...	97	98	95	89
Cereals ...	85	98	90	91
Legumes, dried	78	90	97	88
Sugars and starches ...	—	98	—	98
Vegetables ...	88	95	90	91
Fruits ...	85	90	90	88
Total vegetable foods of mixed diet ...	84	97	—	92
Total food ...	92	97	95	91

(iv) *Roughage*. Though the absorbability is an important guiding principle in the choice of foodstuffs, it is not always an advantage to prescribe a diet which is completely absorbed and does not leave any residue. To ensure the proper action of the bowels, the intestines apparently seem to require a definite amount of ballast or roughage as we now popularly term it. This is particularly true of herbivorous animals which, if fed upon a diet which leaves little or no residue, suffer from affections of the intestines which may prove fatal, whereas such effects can be avoided by adding to the food any material which leaves behind an unabsorbed residue. That this is universally true of man, whose intestine is shorter in proportion and whose food is not strictly vegetable, has been very largely accepted by modern scientists.

(v) *Biological value*. The term biological value is applied to proteins only and its importance in dietetics has only been recently appreciated. By biological value is meant that property of proteins by which they can replace the wear and tear of the body. Thus when it is said that the proteins of milk have a high biological value or those of wheat have a low biological value, it is meant that milk proteins can supply the requisite material for growth at a lower figure for intake than can those of wheat. Proteins of poor biological value have, therefore, to be supplied in larger amounts to counteract the body catabolism than proteins of higher biological value. The biological value of proteins has been expressed in figures. If 100 parts of body protein can be replaced by 100 parts of a food protein then that food is said to have a value of 100. If however 100 parts of it replace only 60 parts of body protein, then it is said to have a value of 60 and so on.

In ordinary dietetics we usually deal with proteins of mixed sources and the quantity consumed is usually sufficient to meet the tissue waste and, therefore, the question of 'biological value' of special proteins does not arise. In the prescription of invalid dietary and under circumstances where life has to be maintained with the minimum quota of protein, the selection of the proper proteins becomes very important. If a protein lacks in the amino acids (lysine, arginine, tryptophane, tyrosine), which are essential to the manufacture of human protein, that protein is absolutely useless to the body economy. For example, gelatin has no tryptophane, no cysteine and very little tyrosine in its composition. Zein, a protein derived from maize, is devoid of lysine and tryptophane. On the whole it has been found out that animal proteins have good supplies of the amino acids in their molecules suitable to the body mechanism while vegetable proteins have considerably less. It, therefore, follows that in

nutrition, animal proteins are more valuable than vegetable proteins. Further, it has been noted that proteins of high biological value raise the biological values of other poorer proteins when taken with them. The function of the cheese, eggs, fish, meat and milk proteins which we take in our diet is to render the vegetable proteins of wheat and other cereals and the pulses of greater value in nutrition than they otherwise would be.

Amount of food required in health. I. *Protein, carbohydrate and fat*:—A good deal of work has been done by physiologists to determine the optimum quantities of the three proximate principles of food, the proteins, carbohydrates and fats, required by human beings for the maintenance of health and efficiency. No definite agreement applicable to the human race as a whole has yet been reached. The body remarkably adapts itself to changes in diet and it will be wrong to apply any hard and fast rule as to what the relations of protein fat and carbohydrate should be. As proteins supply the building material to the body and as a healthy man is always doing a moderate amount of muscular work, the protein quota in food should always be considerably above the loss sustained daily, if a proper balance and growth of the body is to be maintained. It has been assumed, as a result of a large number of observations, that the protein in the diet of an average man should not fall below 80 grammes a day and should contain sufficient quantities of good protein (*i.e.*, of animal origin) to supply 5 per cent. of the total 'calories.'

The carbohydrates and fats in the diet supply the energy required by the body. As far as the demand of the cells for energy is concerned, it is a matter of indifference how much of the total energy required is obtained in each of these forms. To the digestive organs, however, it is by no means a matter of indifference. If all the energy not provided from protein, were to be obtained from carbohydrate, it would mean that a large bulk of food must be consumed, which would not only overload the stomach and intestines but would also be prone to undergo fermentation. If, on the other hand, fat be adopted as the exclusive source of energy, the limits of fat absorption would be overstepped and nausea and diarrhoea produced. The absorbed fat

may cease to be normally metabolised, giving rise to ketosis. Exclusive fat or carbohydrate food, therefore, is not good for the system, though theoretically the required amount of energy can be easily supplied by any one of them individually (much more easily by fats as they have a higher caloric value). The proportion of fat to carbohydrate may, however, vary within a wide range depending upon environment, habit, etc. Thus the Eskimo takes twice as much fat compared with carbohydrate because his environment does not produce plant products; the Indian takes much more carbohydrate than fat because cereals and other articles rich in carbohydrate constituent can be grown easily. It has been estimated that in an optimum diet for persons living in temperate climates, 20 to 35 per cent. of the caloric requirement should be derived from the fats and 55 to 60 per cent. from the carbohydrates.

As a rule, it is appropriate to assume that a man (or woman) who leads a quiet life at home with little exercise requires about 2,500 calories; that if he is engaged in a sedentary occupation, 3,000 calories are required; that if he engages in a moderate amount of exercise or is a labourer doing light work, he can get along on 3,500 calories; and that if he does hard work, 4,000 calories or even more are necessary. Such rough estimates are easy to remember and, while liberal, are sufficiently accurate for most purposes.

Mineral constituents of food. The mineral ingredients of the diet are important building material for the body. This will be evidenced from the fact that the human body contains about 7 lb. of mineral matter.

The chief mineral substances required in the food are sodium, potassium, calcium, magnesium, and iron, along with phosphorus, chlorine, sulphur and traces of silica, fluorine and iodine. Copper must be added to this list, since recent investigations indicate that it is essential for the formation of hæmoglobin. Some of these elements are distributed very unevenly, for 99 per cent. of the calcium and 75 per cent. of the phosphorus is present in the bones, three quarters of the iron is in the red blood corpuscles combined as hæmoglobin and nearly the whole of the iodine is stored in the thyroid gland. Most of the potassium is contained in the cells, whilst most of the sodium is contained in the blood and tissue fluids.

The foodstuffs, proteins, fats and carbohydrates in a pure condition contain only five of the fifteen essential elements, and feeding on a diet free from inorganic substances kills animals within a month and more rapidly than does total starvation. This shows very definitely that the mineral constituents are essential for the maintenance of the fabric of the body.

The mineral constituents cannot supply any heat to the body as they enter the body in a highly oxidised form. They are, however, important in regulating the production of energy in the body. Thus calcium is essential in the production of muscle contraction, whether of the skeletal or the cardiac muscle. Iron is essential for the normal processes of all oxidation and the production of energy by tissue cells, iodine in the production of the secretions of the thyroid gland which govern the body metabolism.

Mineral need of the body. No definite estimate of the quantity of mineral matters required for healthy nutrition can be given. Many of the waste mineral matters of the body are excreted by the intestine, and there is no means of telling what proportion of these has merely escaped absorption, and how much has been excreted from the blood after playing a part in metabolism. A rough estimate of the mineral requirements of the diet in grammes per day is given below (Hutchison and Mattram).

Phosphoric acid	... 3 to 4	Calcium	... 0.4 to 1
Sulphuric acid	... 2 to 3.5	Magnesium	... 0.3 to 0.5
Potassium oxide	... 2 to 3	Chlorine	... 6.0 to 8
Sodium oxide	... 4 to 6	Iron	... 0.015

In the ordinary mixed diet, the amount of mineral matter present is about 20 grammes and, therefore, is usually sufficient for all the needs of the body. Most of the minerals are in a state of organic combination. Thus both calcium and phosphorus are present in organic combination in milk, iron in meat, sulphur in all protein-containing foods and so on. Minerals seem to be utilised in the body much more easily in organic form than in inorganic form, though there is evidence to show that minerals, like calcium and iron, are quite easily absorbed in a purely inorganic form.

Water. It is an essential constituent of all protoplasm and a vitally important factor in the body nutrition. The average water content of the body is about 70 per cent. and this high figure is absolutely necessary to provide the body with a medium in which chemical actions can occur and osmosis and diffusion can effect the necessary transference of chemical compounds through the tissue membranes. It is thus of much greater importance than the ordinary food stuff and is second only to oxygen regarding the proper working of the complex biological

processes inside the animal organism. Since there is a constant loss of water from the body by the kidneys, lungs, sweat glands and bowels, there is a tendency to a greater concentration of chemical compounds in the tissues; but before this can reach a dangerous concentration, the sensation of thirst prompts a replacement of water. This delicate reaction to concentration of the tissue is sufficient to help maintain near its optimum, the balance between water intake and output.

Water may be absorbed into the system through various channels. It is slowly absorbed from the stomach where it also delays the absorption of other substances. It is absorbed readily from the small and large intestines and in these it favours the absorption of substances dissolved in it. In health the absorption mainly takes place from the upper part of the small intestines, the colon only absorbing two-thirds of the water that enters the cæcum. Through the normal intact skin, water is not appreciably absorbed, the outer layer of the mammalian skin may slowly absorb a little quantity, but the passage of significant amounts inwards through the skin does not occur. When ingestion becomes impossible, it is difficult to supply water fast enough through other channels. Rectal administration and parenteral infusion are all inadequate.

The excretion of water occurs mainly by the kidneys, the lungs, the skin and the intestines; and there are many factors which modify the rate of excretion to a considerable extent. Thus if water is taken hot, it favours diaphoresis; if taken in excessive quantity it may lead to diarrhoea and be rapidly eliminated. If it is taken before food, almost an equal amount will be promptly excreted by the kidneys; if it is taken with or soon after food, it may be retained.

The actual rate of turnover of water everyday by the various organs is very interesting. Some of the organs and body fluids such as the salivary glands, stomach, intestinal walls, pancreas, liver and lymph return the water that they drain from the blood. The minimum represented in this way is 3,700 c.cm., a more liberal estimate is 9,800 c.cm. In the case of the kidneys, the colon, the skin with its insensible loss, the sweat glands and in women the mammary glands, the figures for actual total loss of

water from the body range from a minimum of 1,050 c.cm. to the liberal figure 7,800 c.cm. These calculations made by Adolph, permit one to estimate the total daily water turnover at something between 4,700 and 17,600 c.cm., representing an actual possibility of more than four gallons.

The body receives water from various sources—ingested fluids, water contained in solid foods and water produced from the complex chemical processes of metabolism. Water taken along with meals has beneficial effects upon all the digestive organs, provided, of course, the food is well masticated. It aids the digestive action of the saliva, and helps the flow of the gastric as well as the pancreatic juice. It secures better absorption of food, and lessens the putrefactive process of the large intestine.

It would be of special interest in this connection to go into the quantity of water taken daily by the people of the tropics. The various climatic influences demand a more liberal intake of water owing to a comparatively high loss of water from the body due to constant and profuse perspiration.

Saderstrom and DuBois give the data regarding the intake and output of water in the daily life of an average normal individual.

Water intake:—

Drinking water	300 gm.
Water in coffee, milk, soup, etc.	.	..	580 gm.
Water in solid food	720 gm.
Water from oxidation of 100 gm. of protein	41 gm.
Water from oxidation of 110 gm. of fat	118 gm.
Water from oxidation of 244 gm. of carbohydrate	135 gm.
Total			1,894 gm.

Water output:—

By kidneys	750 gm.
By bowels	300 gm.
By skin and respiratory passages	700 gm.
Total			1,750 gm.

Amount retained in the body	144 gm.
Gain in the body-weight	100 gm.

In the tropical climates the figures of both the intake and output are considerably large. Dehydration may result from low water intake or excessive water output, such as may occur in hot climates. Sensation of thirst normally indicates dehydration first, but under certain pathological conditions it may proceed to a dangerous degree before it can be detected. The superficial signs of lack of water are dryness of skin, shrinkage of subcutaneous tissue and diminution in the quantity of urine. In order to find out whether there is adequate supply of water to the body and proper retention, measurement of the body weight is a reliable guiding factor. Most physiologists will agree, however, that all measurements of the state of body with respect to water must be relatively empirical until the mechanism of regulation is better understood.

Dietetic sources of the mineral constituents:—

Calcium. Milk and eggs are the commonest sources of calcium, milk containing 1.5 gm. of lime in every litre. Cheese is very rich in calcium but is not largely consumed in India and probably not in other tropical countries. Foods poor in calcium are meat, fish, bread, fruits and potatoes.

An infant requires about 0.3 gm. (5 grains) of lime daily. The adult, owing to cessation of growth of the bones, requires relatively less (0.4 to 1 gramme). During pregnancy the calcium need of the mother is high for it has been shown that in the last 3 months of pregnancy the foetus requires about 0.3 gm. of calcium a day. The importance of milk and eggs as foods for growing children and during pregnancy and lactation will be apparent from these facts.

Magnesium. Magnesium is usually present in foods in the same proportion as calcium. Milk also contains magnesium and meat more magnesium than calcium.

Iron. Iron is usually present in food in an organic form. It is mainly excreted in the faeces, and hence a definite estimate of the daily amount required by the body is not possible. A normal diet contains about 20 mgm. or more of iron and this quantity is sufficient to meet all physiological demands.

The amount of iron in different foods varies widely. For example, the following quantities of iron in milligrammes per 10 grammes are contained in certain common foods.

Green vegetables	20 to 40
Peas, dried	5.7
Milk	0.2
Beef and eggs	8.0
Rice, polished	0.9

From the results available, it may be concluded that red meats like mutton and beef, and yolk of eggs are very rich in iron, as also vegetable foods like rice, potatoes, spinach, wheat. As regards an ordinary mixed diet, it may be said that the amount of iron which it contains is roughly proportional to its richness in protein, for these two constituents tend to run parallel to each other.

An abundant supply of this metal is of special importance to growing children and to women during pregnancy. The new born infant starts life with a fairly rich store of iron from the mother, and as long as its sole food is milk, it lives on an iron-poor diet.

Sodium and potassium. Sodium is obtainable from the animal group of foods whereas potassium is contained chiefly in the vegetable group. Sodium is absorbed in the form of sodium chloride and, as is well known, this is consumed to a much greater extent than is ever required by the body. The minimum requirement of these salts is from 1–2 gm. per diem but an ordinary mixed diet contains 3 or 4 times this amount and hence deficiency in these salts is not likely to occur.

Phosphorus. Phosphorus enters into the composition of all cell nuclei and it is abundantly present in the bones and in the central nervous system. Wherever growth is going on rapidly a large supply of phosphorus will be required in the food, otherwise development will be seriously impaired. The phosphorus contained in foods is for the most part present in an organic form, part in inorganic form as phosphates of the alkalis or alkaline earths. There is reason to believe that the organic forms are more valuable for contributing to the growth and repair of the tissues; nucleoproteins (liver, kidney, sweetbread), phospho-proteins (milk, cheese, yolk of egg), lecithin (yolk of egg), and other phosphatids and phytin (hexaphosphoric ester of inositol and is found in bran, leguminous seeds and tubers) are all rich sources of organic phosphorus. Fresh vegetables are also good sources of phosphorus.

Sulphur is present in organic combination chiefly in proteins.

Chlorine is ingested almost entirely in the form of sodium chloride.

Iodine is present in small quantities in fresh water plants, water and land plants. The amount required in the diet daily is estimated to be about 45 microgrammes for an adult and 150 microgrammes for a child.

Fluorine and **silica** are present in the body in small quantities chiefly in the teeth and bones. Vegetable foods and especially the cereals, are the most abundant available sources.

A satisfactory diet. A healthy diet, therefore, must contain suitable quantities of:

- (a) Proteins which should be digestible and absorbable and which should have a positive biological value.
- (b) Carbohydrates.
- (c) Fats.

- (d) Mineral constituents including salts, iodine, etc.
- (e) Vitamins
- (f) Water.
- (g) A sufficient roughage.

The diet must also be free from poisonous substances. Certain individuals are particularly sensitive to certain articles of diet and these should be particularly avoided to avert the unpleasant and sometimes dangerous anaphylactic symptoms.

Taking a broad view, one can safely regard a diet as being suitable when large groups of human beings who have lived on it for generations, are healthy and long-lived. The Sikhs of the Punjab attain to perfect physical development on a diet which is quite different from that which is adopted by Europeans. There is a school of physiologists who think that people who are predominantly vegetarians are likely to be more under-developed and short-lived than those who eat considerable quantities of meat. Practical experience of Asiatic races, who are mainly vegetarians, however, does not bear out the contention of these physiologists, as some of these races are just as healthy and long lived as the people of the West who take much larger quantities of animal food. It must not be forgotten that the so-called 'vegetarians' are not truly speaking vegetarians as they usually take milk, which is a product of animal origin. The relative merits of vegetable and meat diet have been set forth by different schools of thought and it will not serve any useful purpose to enter into a detailed description of the points which have been raised in this connection. Whatever may prove in the end to be the best for an ordinary adult, who has great powers of adaptability, there can be no doubt that in the case of children, adolescents and pregnant women, it is far safer to adopt a high protein standard than a low one. No risk must be run of providing too little building material for the growing organism.

THE INDIAN DIETARY

It will be interesting in this connection to consider the dietary of Indians and to see how far this diet comes up to the satisfactory standard. The importance that the Indian ryot attaches to his diet is hardly realised by Western practitioners. It is not uncommon to find a practitioner writing up prescriptions for medicines without any directions as to the nature of the diet his patient should take. The patients often remain dissatisfied in this respect and may lose faith in the physician.

The Indian diet has largely been founded on economic principles but also partly on the long experience of climate.

on social customs, etc., and is now a sound working principle based on a fight against the poor nature of the soil, and the paucity of rains. Two meals are eaten during the day, the morning meal generally consisting of rice and *dal* (pulses) or unleavened bread and curdled milk; the next meal consists of rice with *dal* or vegetables, or unleavened bread with vegetables or meat curry. In villages, the ryot often drinks diluted milk, or curds. In towns during the hot weather some savoury food is taken during the afternoon. Indians are very partial to fruit and in Northern India fruit is eaten before or between these meals. Meat is rarely taken more than twice a week but amongst Brahmins, Buddhists and Jains, meat is not eaten in any form. The nitrogenous portion of the diet is largely made up by milk and *dals* or pulses. We will now discuss these diets in some detail and try to show how far these items of diet supply the necessary proximate principles.

The carbohydrates. The staple food of the people of India is rice. According to the report of the Famine Commission, out of 191 millions people in the country, nearly 68 millions are rice eaters. In the Punjab, U. P., and Oudh, in Behar, the northern parts of the Central Provinces, and in Gujrat (Kathiawar) the poorer classes live on the millets grown in the rains, and on barley and gram; the richer classes eat principally wheat or rice. In Bengal proper, Orissa, and the eastern portion of Central India, rice is the principal food; In the South, in Bombay and the northern parts of Madras, the two varieties of large millets (*jowar* and *bajara*) form the principal food. In Mysore the ordinary food is the small variety *ragi* but rice and wheat are also taken. Baluchistan, the North-Western Frontier Province and in the higher Himalayas a good deal of maize flour is also eaten along with a certain amount of rice.

The carbohydrate food of the Indians, therefore, can be divided into two types:—

(A) Rice—in the rice-growing areas of Bengal, Madras, Southern India and in sub-montane areas of Nepal, Kashmir, and British India.

(B) Flour—as unleavened cakes (*chapatties*). The bread is made from wheat in the Punjab, millets over Central and Southern India and from maize in the N.W.F. Province, and Bihar.

Sugary foods. Sugar is obtained in India from the sugar-cane and to a small extent from various palms, e.g., the date. Coarse sugar (*jaggery* or *gur*) is largely used by the poor classes whereas all sorts

of refined sugars (e.g., *chini*, *misri*) are taken by the richer sections of the population. The Indians are particularly fond of sweet things, and if they can afford it, will consume a considerable amount of sugar during the day.

The variety of sweets eaten are enormous and consist of mixtures of sugar with different preparations of milk, curds, rice, *sufi*, flour, cocoanut. Milk is often sweetened with sugar before taking.

The proteins. (a) *Milk and Milk derivatives.* Milk is the most popular protein consumed in India. As a matter of fact cow's milk is the staple food of the ryot in most of the rural districts of India. In towns, most of the milk sold is a mixture of cow's and buffalo's milk well diluted with water. Cow's milk is considered to be strength building, fattening and beneficial in gastric conditions. Buffalo's milk, goat's milk, etc., are also used in different parts of India.

Dahi or curdled milk is one of the most important milk derivatives. It is nothing but ordinary milk which has been allowed to undergo lactic acid fermentation and coagulates into a creamy white gelatinous mass like junket and has a pleasant acid taste. Curdled milk is better borne by the stomach as it has been already coagulated and its thick consistency makes it possible to be broken up by mastication. Its acid taste makes it more refreshing than milk and when diluted it makes a delicious cool drink in the hot weather. Metchnikoff's view of introducing into the alimentary canal bacteria that will inhibit the proteolytic action of the organism of putrefaction by virtue of the lactic acid produced by them, seems to have some support by this universal custom of taking curdled milk. *Potcheese (chhana)* is made by coagulating milk by citric acid, i.e., the juice of the lemons and removing the whey. It must be used fresh as it deteriorates very quickly. Whey (*ghol*) is a greenish yellow coloured liquid with a sweet acid taste. Whey contains lactose and lactalbumin and is devoid of albuminoids so that it is easily assimilated. Butter-milk is the liquid that is obtained after the milk has fermented and the fat has been churned off as butter. It is called *chachh* (U.P.) or *lassi* (Punjab) and is largely drunk in Northern India. Being fat free, it should be useful in hepatitis, jaundice and sprue.

(b) *Meat.* Meat is undoubtedly the most assimilable form of protein in the food. The religious practices and social customs existing in India are sometimes great obstacles to meat eating. Thus the Brahmins, Jains and Buddhists are prevented from eating meat by their religion. Generally speaking, meat is used sparingly in India. Beef is used only by the Mohammedans and foreigners in India; mutton is more commonly used by the Hindus. The meats of the domestic fowls and wild game birds are also sparingly used. The Hindus in some parts abstain from taking the meat of domestic fowls, but are allowed to eat game.

(c) *Fishes*. There are numerous species found in the Indian rivers; these vary in quality; some are of fine flavour (*Hilsa*, *Mrigal*, *Katla* and other fat fish) while others are poorer in quality (*Koi*, *Singhee*, and other lean fish). Fish is an important article of food in Bengal where very little meat is taken. Sea fish is taken by certain sections of the population living along the coasts.

(d) *The 'pulses' or 'dals'*. The pulses largely supply the nitrogenous constituent of the diet of Indians. Various kinds of pulses are grown all over India and are available at a cheap price. The dals may be taken in various ways, many of them are cooked in the green unripe state as a vegetable. When dried and ripe, the pulses may be cooked as a *puree* with the addition of some ghee. The pulses contain larger quantities of proteins and in many cases make up for the deficiency in foods such as rice.

Fats. *Ghee*. Clarified butter or ghee is the commonest fatty substance taken in this country. Butter is made from milk-fat obtained by churning which mechanically ruptures the albuminoid envelopes surrounding the fat droplets and allows them to come to the surface. This butter is clarified by heat and is then known as ghee. Ghee is used by all classes of people who can afford it, in the preparation of vegetables, curries, etc., and enters into the composition of many of their sweets and pastries.

Sesame oil. The oil from the seeds of *Sesamum indicum* (til) is used in some parts. This oil, however, is expensive and is not much used in cookery.

Cocconut oil is a fixed fatty oil with a specific gravity of 0.892. The bulk of oil is obtained by cold expression from copra. In Southern India especially in Cochin and Travancore, it is used extensively in cooking.

Mustard oil is obtained by pressing the seeds of the mustard (*Sinapis nigra*). It is largely used in Bengal and in other parts for cooking purposes. The oil must be heated at first to destroy the action of the ferment myrosin and to remove the volatile pungent essential oil. *Walnut oil* is largely used in Kashmir for cooking purposes.

For further information regarding the cereals, pulses, edible oils, etc., used in India, see Appendix.

Errors of Diets in the Tropics

Overfeeding. It is perhaps no exaggeration to say that the tendency of civilised people, and especially of the upper classes in civilised society, is to eat more than the necessary minimum. A moderate excess of food is probably harmless, if not actually beneficial. For it is well to have some reserve in the body which can be called upon in cases of emergency. This limit,

however, is frequently overstepped by the well-to-do people in the tropics. The nature of the diet in the tropics is predominantly of vegetable origin and contains plenty of carbohydrates. The general results of habitual or chronic overfeeding with such bulky carbohydrate food are pendulous abdomen and obesity. The sedentary habit of the majority of people further helps in diminishing tissue catabolism and consequent deposition of fat. Obesity is one of the commonest end-results of overfeeding.

Excess of carbohydrate in dietary. An important dietetic error which prevails among the richer sections of the Indian population is the excessive consumption of carbohydrates and sugars. Bengal seems to be the worst offender in this respect and it is not uncommon to find an average man taking sweetmeats in large quantities both with the morning and the evening meals. The rich man who can afford more, usually takes more of these things. This large carbohydrate intake causes a good deal of strain on the digestive organs and hence gastrointestinal disturbances are quite common in the tropics. Considerable strain is put on the internal secretion of the pancreas which is primarily concerned in the metabolism of the carbohydrates. When this carbohydrate intake is carried on for a very long time, obesity and diabetes result. In some of the well-to-do Bengali families of Calcutta it is the rule rather than the exception for the males to have alimentary glycosuria or frank diabetes before reaching the age of fifty years. Though excessive carbohydrate ingestion may not be the only cause of this high incidence of diabetes in the tropics, this factor is certainly one of the most important causative agents. The sedentary habit is also another factor which cannot be ignored.

Protein shortage in the diet. McCay pointed out that the Bengalis and many of the other races in India suffer from nutritional defects which are associated with the unsuitability of their diet; they are undersized, the average weight being only 50 kilogrammes; their capacity for physical work and their resistance to disease are low; even the kidneys, which might be expected to be healthy, are very liable to degenerative changes in the parenchyma, which result from the lack of nitrogen in

the blood. According to McCay, all these defects are due to the shortage of available proteins in the diet of the Bengalis. When excessive quantities of rice are eaten, the absorption of proteins is seriously interfered with, for example, he found that 8.5 gm. of protein were absorbed when 19 oz. of rice were eaten daily, whereas only 6.5 gm. were absorbed when 30 oz. were eaten. It is, therefore, impossible to make up for the low percentage of proteins in rice by eating large quantities. He also found that the vegetable sources of proteins are often unsatisfactory and these proteins are absorbed much more slowly than the animal proteins. The deficiency of protein in the Indian dietary has also been stressed by a large number of Indian workers. As proteins cannot be stored in the body and kept as a reserve supply for times of emergency, it is only proper that the daily protein intake should not fall to a very low level as is the case with many Indian dietaries.

In general, bodily activity is reduced in the tropics and the digestive powers are undoubtedly not so vigorous as in cold climates. The European coming out to Eastern countries cannot easily give up the dietary habits and tendencies of a temperate climate. A high protein diet which is wholesome and perhaps a necessity in cold countries may actually prove injurious in the tropics. Proteins have a high specific dynamic action and a diet which includes proteins in excess is naturally a 'heating diet.' In hot weather, the production of excessive heat inside the body may be not only uncomfortable but may be actually injurious by taxing the peripheral circulation and sweat glands in the necessity of transferring the body heat to the hot humid air.

Further a predominantly protein diet is likely to leave a very imperfect residue as such diet is always better absorbed. In the tropics the general musculature of the body as well as the intestinal muscles are not kept in that tone which is common in the residents of the cold countries and, hence, constipation results. Habitual constipation leads to intestinal stasis and the absorption of toxic end-products of protein cleavage. Gradually the constitution gets undermined, bowel troubles supervene and mental disturbances in the form of neu-

raesthesia, failure of memory, irritability, etc., result. It is also probable that sprue and appendicitis, so commonly seen amongst the Europeans and so markedly absent in the indigenous races of the tropics, have some relation with auto-intoxication from the bowels.

Alcohol. Indulgence in alcohol is another factor which may advantageously be considered under this section. Though alcohol is not an article of food, it is commonly taken as a drink along with food and this is perhaps one of the most important dietetic errors in the tropics. The Europeans suffer most from the alcohol habit though in recent times, a good section of the Indian community also has contracted the habit. The plea usually put forward is that alcohol is necessary for the maintenance of health and that without its stimulating influence, no strenuous work can be carried on satisfactorily. Others consider it a stimulant which is necessary in the tropics after a day's hard work. It is also believed to be a protective from malaria, and bowel and other diseases. These ideas have all been shown to be erroneous. Though one cannot deny to alcohol the right to be regarded as a 'food' in the scientific sense of the term, it cannot be regarded as a food of great importance, for although it is able to replace fat and carbohydrate it cannot be converted into these, while its secondary effects on the nervous and vascular systems counteract, to a large extent, the benefits derived from the production of heat and energy by its oxidation. Many writers have produced evidence to show that it is not favourable to the production of healthy brain work and mental labour. Alcohol has no influence on physical labour and sustained muscular effort as is generally supposed. It may even do harm by paralysing the sense of fatigue which is the natural check on excessive exertion.

On the other hand, whenever the proportion of alcohol circulating in the blood becomes greater than the cells can rapidly deal with, it acts as a protoplasmic poison. The brain cells seem to be peculiarly sensitive to the paralysing action of alcohol, so that the brain is the first to show the effects of an overdose and intoxication results. If this overdosage is kept up for a very long time, the highly organised and delicate brain

cells would naturally become the seat of various degenerative changes. A certain degree of dulling or even paralysis of the moral perceptions has been noticed in chronic alcoholics by many observers. Apart from its bad effects on the brain centres, the presence of undecomposed alcohol leads to a diminution of the chemical energy of the cells which interferes with the ordinary course of metabolism and may result in chronic disease. The metabolism of fat is most likely to be interrupted and hence alcoholism is a common cause of fatty degeneration.

The excretion of undecomposed alcohol through the kidneys may also act as an irritant and bring about changes in structure and ultimately may produce chronic nephritis. It has injurious effects on the gastro-intestinal tract and particularly on the liver. Alcohol also paralyses the blood vessels and thus interferes with dissipation of heat from the body. It renders people liable to heat stroke and alcoholism is one of the prolific causes of this condition in the tropics.

It will thus be seen that alcohol is an unnecessary article of diet in normal health and is not truly beneficial to the system but is actually injurious from the physiological point of view. Alcohol, there is little doubt, is a potent factor in shortening the life and undermining the health of the majority of Europeans in the tropics. Alcohol strongly predisposes to liver abscess, heat stroke and tropical neurasthenia. It makes the habitue a bad subject for surgical operations and lowers the resistance of the tissues to intercurrent infections. Obesity, diabetes and other disorders of metabolism like gout, etc., have all been ascribed to the excessive ingestion of alcohol.

DIET IN DISEASE

Diet plays a very important part in the treatment of disease in the tropics. Diet may be considered in the light of a therapeutic agent and, like all other remedial agents, has a limited place in therapeutics and should not be considered as a panacea for all ailments. Dietetic treatment is specially important in a particular group of disorders and we will confine our attention to these disorders primarily. The

principles of feeding will only be outlined, the detailed regime will naturally have to be laid down by the physicians with special reference to the particular type of requirement.

The prejudices of patients and the superstitious beliefs existing in India sometime make it very difficult for the physicians to prescribe a regular routine of diet according to strict scientific principles. Thus milk is regarded in some parts of India as injurious to those who have got a cough as it is supposed to increase the phlegm. In some places, it is forbidden in cases of diarrhoea. In prescribing diet these prejudices and beliefs have to be attended to. Individual susceptibility to various foods should also be taken into account.

Diet in fever. The pathological conception regarding the production of fever has undergone a radical change within recent times. In the time of Hippocrates and long afterwards, fever was supposed to originate from bad humour and intestinal irritation and hence the principle of diet was either to starve the patient or to allow only such bland non-irritating and harmless articles, *e.g.*, thin barley gruel and old wine which will allay intestinal irritation and thereby diminish the range of the temperature. A revolt against this starvation diet was not, however, late in making itself manifest and a second school of thought promulgated the idea that fevers were asthenic diseases and should be treated with liberal feeding rather than starvation. Though this doctrine has never been adopted *in toto* in practice, it must be admitted, in the light of our present knowledge of the metabolic changes in fever, that the plan of 'feeding fevers' is a much more rational and sound plan than starvation diet. Thus it has been observed on many occasions that the free administration of food does not, as was formerly supposed, tend to raise the temperature of feverish patients. Von Hoesslin found that in cases of typhoid the temperature during the days when food was administered was only from 0.11°C . to 0.3°C . higher than on starvation days. Moreover, the absorption of light articles of diet goes on as perfectly in the febrile as in the non-febrile state. There is, therefore, no reason why a fever patient should not be allowed to have sufficient food.

up to the limit of his digestive capacity which is greatly interfered with during febrile conditions.

From a study of the metabolic changes, the chief dietetic indication in general fevers, therefore, is to supply a large proportion of protein in the diet to counteract the active protein loss. Though this appears quite a simple matter theoretically, it has been observed that it is impossible to bring about a condition of nitrogenous equilibrium in acute fevers. The noxious action of the toxins on the tissue cells renders them incapable of assimilating proteins, so that the administration of protein diet during febrile stages instead of repairing the breakdown, actually does harm by flooding the circulation with protein cleavage products which are toxic to the liver and the kidneys. It is not logical, therefore, to give too much protein ration to fever patients. Carbohydrates and fats are known to be 'fever protein-sparers' under certain circumstances and the tissue breakdown in fever can only be stopped by supplying these in abundance. Then again, fats are not liked by fever patients probably because they are not readily digested. The carbohydrates, therefore, are our mainstay in dieting fever patients.

General scheme of diet. For purposes of dieting it is necessary to secure such a state of affairs as will coax the appetite, create relish for such insipid food as may be allowed and a clear state of the gastro-intestinal tract. A fluid diet is considered the best by common consent. This evades the necessity for chewing which is rendered difficult by the diminution of the salivary secretion and also relieves the thirst and supplies plenty of fluid to the parched tissues. Milk is the simplest, most accessible and most nutritious of fluid foods and should always form the basis of the dietary. Plenty of fluid drinks may also be allowed. Some workers claim that saline-containing beverages are better than ordinary drinks as these may replace the salts which are rapidly excreted from the kidneys during fever. Such a claim, however, has no real value. The kidneys have the power of re-absorbing through the tubules the salts necessary for tissue metabolism and if we assume that the kidneys are in a healthy condition, there is no reason to

think that the mineral constituents of the cells have drained away through them and that replenishing is necessary through the mouth.

A common mistake in tropical countries, particularly in the summer season, is to allow iced drinks. Though there is no evidence to show that these are injurious in any way, they have been frequently observed to give rise to a congestion of the throat and a distension of the stomach. The excessive consumption of aerated beverages is to be avoided, as tending to overdistend the stomach with gas. The water of unripe coconut (*dab*) is a very pleasant drink available in the tropics and may be allowed if the patient cares to have it.

The system requires much less energy to maintain it at a normal level while in rest than when it is carrying on some muscular work. As all the fever patients usually remain in bed, the caloric requirement is also small. It has been estimated that for an adult human being of average weight, nearly 1700 calories are required in the resting condition to keep it in balance. If four pints of milk are consumed in a day, the necessary caloric value is obtained and there is no necessity to worry about the tissue break-down. If, however, this is not taken for some reason or other, the milk should be fortified. The amount of protein in it may be increased by the addition of such preparations as Plasmon or the proportion of fat may be raised by the addition of cream. It is better, for reasons already adduced, to enrich the milk with carbohydrates like glucose, milk-sugar, cereal preparations like arrowroot, oat flour, corn-flour, barley, sago, *sati*, rice-gruel, etc. Fruit juices like that of orange, pomegranate, grapes, pine-apple, pears, apples, jamrook, etc., may also be given in moderate quantities. Sugarcane is a very good thing in India if the patient is not too weak to chew it. It cleanses the mouth and the juice is very refreshing. In addition to these, soups, beef tea, thin pea or *dal* soup or broths, may be allowed in the proportion of about one pint a day but these are better avoided particularly when diarrhoea is present.

Use of alcohol in fevers. Alcohol is undoubtedly of value in febrile states if it is used in moderation and according to

the direction of the physician. Its properties as an indirect stimulant to the heart is too well known to need any special mention and in fevers which are asthenic conditions, a stimulant in any form should be helpful. Alcohol reduces body temperature by dilating the blood vessels of the skin and diminishes tissue waste specially the waste of fat and these properties should mark it out as an agent of great value in fever. It is absorbed immediately and the tissues can use it as a ready source of energy.

Alcohol has been largely used in conditions of failing circulation in fever which are characterised by a quick, weak and irregular pulse. In nervous prostration and sleeplessness also it has been highly spoken of when the digestive powers are very weak, the property of alcohol to spare the tissues can also be utilised. In cases of hyperpyrexia its use has often been attended with very gratifying results.

Diet during pregnancy. Pregnancy is a natural physiological process, and minor ailments associated with it, such as morning sickness, etc., should not be regarded as pathological. The general health of the average pregnant woman, however, in these days, is poor and she is often considered to be an invalid at such times. A large amount of sickness and disability associated with child bearing is due to our lack of knowledge of the relationship of the nutrition of the mother to the normal functioning of her organs. The serious consequences of a deficiency in many essential food substances and with a pregnancy superadded may be greatly reduced by judicious dieting. This problem does not affect the mother alone, the growing foetus also suffers serious results.

The early foetal growth takes place at the expense of the maternal tissue and there is always an extravagant breaking down of it to enable the foetus to get its requirements. At a later stage the foetus derives its nutrition from maternal food. Over and above this, many chemical substances which are essential for its growth are present only in small quantities in maternal organs and they cannot be synthesised by either the mother or the foetus. A liberal supply of these substances (or their effective precursors) must be from the food the mother

takes. Ordinary diets vary widely so far as the energy bearing factors, the proteins, the fats and the carbohydrates are concerned, and yet they may remain compatible with good maternal and foetal health. The trouble arises, when there is unbalanced dietary and a deficiency of factors essential to proper structure, function and even to life of the mother and of the offspring. Among these are calcium, phosphorus, iodine, iron and vitamins A and D. A pregnant and lactating woman has to supply calcium to the foetus from her own store. Calcium and phosphorus of different foods are retained by the body to different extent and the retention is greatly influenced by the presence of vitamin D. Cereals such as oatmeals and cereal embryo which are rich in calcium and phosphorus are anticalcifying and along with them a well-balanced amount of calcium-retaining factor in form of milk and cod-liver oil (which ensures a good supply of vitamin D) should be ingested. Cod-liver oil also supplies vitamin A which increases the resistance to infection.

The significance of supplying iron to the pregnant mother is that the foetus takes away iron from the mother in order to enable it to store iron in the liver to tide over the milk diet period, when it gets a deficient amount of iron. Consequently a failure to supply mother at such a time with sufficient iron will tell upon herself and the child as well. The daily diet should consist of food rich in iron, such as meat, egg-yolk, calf's liver, green vegetables, etc.

Iodine is of importance both to the mother and the offspring. A deficiency of iodine in pregnancy results in cretinism in the offspring and simple goitre or myxoedema may follow numerous pregnancies in a mother. Sea fish or any kind of living matter from the sea and cod-liver oil should be included in the diet.

According to Mellanby "the diet of pregnancy and lactation ought to include the following:

2 pints of milk daily.

1 or 2 substantial servings of green vegetables—cabbage, spinach or lettuce daily.

1 or 2 eggs or egg-yolks daily.

An apple or orange or some fresh fruit daily.

Sea fish twice or more a week.

Cod-liver oil may be taken 2 teaspoonfuls daily.

The rest of the diet can be made up as the expectant mother desires."

Green-Armytage recommends for the Indians, the following diet with the addition of radiostoleum and Parrish's food.

Cereals	.	<i>Dhenki</i> (home-pounded) rice; <i>atta</i> (whole meal flour) and <i>sujl</i> .
Vegetables	..	<i>Sak</i> (green leafy vegetables) in all forms except fried. <i>Sabji</i> (green vegetables, etc.), bean, pumpkins, cucumber, brinjal, green peas, squash, cabbage, cauliflower, tomato, etc.
Fruits	...	All, fresh or stewed.
Eggs	..	Ducks or hens in any form except fried.
Fish	...	Mud fish like— <i>kai</i> , <i>magur</i> , <i>singee</i> .
Meat	..	Mutton, chicken, liver, kidney, etc.
Fats	...	Oils, butter, ghee—sparingly.
Milk	...	Fresh goat's or cow's in any form—plain, <i>dahi</i> or <i>ghol</i> . Avoid buffalo's milk.
Sweets	..	Honey, molasses, jam, jelly, marmalade. No pastry, no cakes.
Fluids	...	Water ad lib., cocoanut water, weak tea, coffee, aerated water, home-made lemonade or lime juice.

It is important to avoid any excess in the individual articles of diet as well as in the total intake of food. The idea that a pregnant woman needs large quantities of food is erroneous. Excess of fat in the diet should be avoided not only during the early months when vomiting is a troublesome symptom, but also during the subsequent months of pregnancy. Vomiting is due at least in part, to excessive fat intake which must be limited.

The position regarding the relationship between diet and toxæmias of pregnancy has been summarised by Mellanby. He says, "It is unfortunate that there is no established clinical or experimental evidence that malnutrition is responsible for those toxæmias of pregnancy which include albuminuria, pre-eclamptic toxæmia, and eclampsia itself. In spite of the absence of such evidence I wish to plead that future investigators of these problems will give some attention to this aspect of the case. The hypothesis that such toxæmias are due to the production of toxic substances by the fetus and placenta has not been fruitful. On the other hand,

there is every indication that they are due to abnormal metabolism and, since so many defects in metabolism are now known to be nutritional in origin, the chances that such a factor is the basis of eclamptic conditions are large.

The final teaching based on the foregoing facts is that proper nutrition is essential to healthy childbearing and that the diet should include throughout pregnancy and lactation a sufficiency of what are known as protective foodstuffs. When plenty of these are taken, there is every reason to believe that the rest of the diet will take care of itself."

In abnormal cases, the diet can be dealt with under the following headings :—

1. Constipation—It is often benefited by increasing fluid intake and the amount of fruit and vegetables in the diet. It is better to avoid taking purgatives of drastic griping type. Saline aperients or lubricants might be used with good results, if at all needed.

2. Albuminuria—In pre-eclamptic cases the dieting should be drastic, the solid part of the diet being epsom salts and glucose and the liquid part water. In milder cases, if they respond to a few days' treatment in bed, on a rigid diet, the pregnancy may be allowed to continue; but the diet should be absolutely protein free. Fruits and vegetables can be taken freely, and milk, cooked in any form, is well tolerated.

3. Pyelitis appears about the 20th week and frequently simulate appendicitis. Massive doses of alkalies with a ketogenic diet often help the patient to tide over an attack.

Diet during lactation. During lactation, the regulation of mother's life is of the utmost importance. The diet should be of plain nutritious food. An ordinary well-balanced diet is best for producing a good supply of milk during lactation period. There are no galactagogues known to be of positive value. In cases where milk is poor or deficient in quantity, thick malt extracts, a table-spoonful three times a day may be prescribed. Where the fat is deficient, plenty of butter, cream and olive oil may be added to diet.

Hoobler has found that diets containing milk proteins and animal proteins are better for producing milk than those contain-

ing vegetable proteins. Over-feeding never increases the quantity of milk. Cow's milk protein is the best form to increase the milk production and to protect the mother's tissue. Besides the food factor plenty of rest and daily bath, a daily walk in open air and as much outdoor life as possible are essential. Tea or coffee should be taken in moderation and anything containing vinegar, spices, mustard, or rich and complicated dishes should be avoided.

Diet during infancy and childhood. It is seldom, if ever, necessary to have recourse to any artificial means of nourishing the newly-born infant. It is the baby's birth-right to be nursed by its own mother and breast feeding is always the best for both the mother and the child. It gives the greatest security against intestinal disturbances and infection which are the commonest troubles with the new-born. The child is more strong and vigorous as compared to those artificially fed and better adapted to surroundings.

When for some condition or other either with the mother or the child, breast feeding is contraindicated, the baby may be fed artificially. There is, however, no perfect substitute for breast milk. Although the results of careful artificial feeding are satisfactory, the problem is beset with difficulty. When a child is called upon to digest food of a different form and build up the body from materials of different quality, he naturally starts at a disadvantage. The younger the child, the greater is the difficulty. Before substituting any form of artificial food for mother's milk, the following points should be considered very carefully.

1. The choice of food.
2. The method of preparations.
3. The amount of food required in twenty-four hours.
4. The size of each feed.
5. The interval between each feed.

Cow's milk, goat's milk and ass's milk may be used for the purpose and of these, the cow's is the most generally used. From a comparison between the composition of cow's milk and that of breast milk it appears that cow's milk contains a large ~~excess~~ of protein and salts but too little sugar; the fat is in

about the same proportion. In order to make it of the same proportion as the human milk, it should be diluted with water and some fat and sugar be added to it. One heaped tablespoonful of sugar of milk and half an ounce of cream, added to half a pint of cow's milk, and made up to a pint with water is, however, a good substitute.

Not all infants, even if normal and healthy, can be fed in the same way. The food should be modified as regards the quantity of each ingredient—fat, sugar and protein, in such a way, as to suit the requirements of the individual child

As regards the amount at each feed, it is customary to begin with 3 ounces; this may be raised to 4 ounces at the end of first month, $4\frac{1}{2}$ during second month and so on. Approximately a child will take 1 to 2 ounces more at a feed for every month of age till 8 or 9 ounces.

Intervals between each feed may be four hours but what is the most essential is the regularity. The child should never be waked up at night for its feeds.

Various patent milk preparations are on the market but these should be avoided whenever possible. None of them are well balanced, all have vitamin deficiency, and many contain excess of fat which gives rise to infantile liver or gastro-enteritis in children.

It is sometimes very useful to add some additional factors to the artificial diet. Cod-liver oil should be started at three or four months in amount of 5 to 20 drops twice daily and continued till the age of eighteen months. Fruit juice should also be added at least two teaspoonfuls daily and gradually increased.

Indications for special modifications. 1. Flatulence and habitual colic are invariably due to over-feeding—the food being given very rapidly, most often at too frequent intervals.

2. Curds in stool—This is generally caused by feeding the baby on an unsuitable mixture or when the digestive power of the child is weak. The difficulty may be remedied by boiling the milk and dilution.

3. Vomiting, loss of appetite, constipation and diarrhoea are other difficulties in artificial feeding and they can always be dealt with by attaining the proportion of all the ingredients.

Feeding of older children. A knowledge of nutrition of a growing child as regards both the amount and kind of food necessary for proper growth and maintenance of health is very essential. The points to be noted in this connection are—

Its constitution, *i.e.*, (a) vitamin, (b) salts, (c) proteins, (d) fats, (e) carbohydrates and (f) water.

The forms in which these elements are to be provided.

The relative proportions of the various elements and the total daily amount of each.

Under modern conditions we are faced with the difficulty of formulating a well-balanced dietary for children.

The ideal diet consists of fresh milk, cream, butter, cheese, curds, eggs, etc.

Cereals	Wholemeal flour, wheat or rye—given in form of bread or cakes.
Vegetables	Green vegetables and tubers.
Fruits	Oranges, apples, plums, bananas, etc.
Sugar	Pure honey.
Meat foods ...	Lamb, chicken, rabbit, calves' liver may be given occasionally.

In the ordinary way the diet is laid down empirically and attention is given to the quality of the food, the quantity being determined in a healthy child by the appetite. The real test of the value of a diet is its clinical results.

The estimated requirement which determines the necessity of a generous supply of food throughout childhood and one relatively in excess of that required for the adult, may be quoted shortly as follows:—45 calories per pound body weight at one year, gradually decreasing to 36 calories per pound at six years and remaining at this figure until puberty.

VITAMINS

The subject of vitamins is new but is rapidly growing. A large amount of literature has been amassed during the last decade and more is coming. A good deal of confusion which once attached itself to the subject has now been cleared up and

vitamins have now earned a lasting place in therapeutics. As with everything new in therapeutics, vitamin preparations are becoming a craze with the medical profession and are being regarded as a panacea for most of the dietary evils of humanity. It is necessary to emphasize that the problems of nutrition must not be viewed from a too 'vitaminic' outlook. Vitamins are certainly important in nutrition and in the maintenance of normal health, but it is only one link in a chain of essential substances requisite for the harmonious regulation of the chemical processes of healthy cellular action. The diet of most of the tropical races is extremely ill-balanced and one-sided; hence it is essential for all students of tropical medicine to have a general knowledge of the value, properties and distribution of these 'accessory food factors.'

Evolution of the knowledge of vitamins. It has long been recognised that the diet must represent not only a certain amount of calories but that it must include certain proximate principles in the form of proteins, carbohydrates, fats, etc. Magendie, before 1820, appears to have been the first to demonstrate the indispensability of protein food. He showed that dogs fed on exclusive diets, such as sugar, olive oil or butter, became emaciated, developed perforating corneal ulcers and died in three to five weeks. It became known quite early that one-sided diets are likely to result in general malnutrition and special diseases such as scurvy, rickets, etc. Early in the eighteenth century, it was recognised that green vegetables or the juice of citrus fruits were the only agents which could cure or prevent scurvy. As early as 1600 A.D., lemon juice was used with success to prevent scurvy in sailors, and in the eighteenth century, Lind definitely showed that scurvy could be prevented by the use of lime juice.

During the latter half of the nineteenth century, beri-beri spread in all rice-eating countries. Takaki of the Japanese Navy thought that the disease was caused by errors in dietary and in 1885, he reformed the naval diet by adding more meat and substituting barley for a part of the rice which had previously been the principal article of food. These changes were very successful and beri-beri practically disappeared from the

Japanese Navy. Eijkman (1890) working in the East Indies found that by feeding fowls on polished rice, a polyneuritis closely resembling beri-beri could be produced. This polyneuritis could be prevented or cured by giving the fowls small quantities of rice-polishings or its extracts.

The existence of two deficiency diseases was thus established by the end of the nineteenth century. Although experience of these deficiency diseases was quite old and although scurvy was recognised as early as the eighteenth century, yet the existence of vitamins was first demonstrated by Sir Gowland Hopkins as recently as 1912. This discovery stimulated an enormous amount of research and by 1918, it was recognised that at least three separate vitamins existed and that the presence of all these in the diet was essential for the maintenance of life.

Vitamins. The works of Hopkins, Funk, Osborne and Mendell and a host of other scientists have shown very clearly that a diet may contain suitable quantities of all the well-recognised constituents, and yet be incapable of maintaining the body in a healthy condition. Vitamins are those remarkable food components, of which minute quantities must be supplied if normal growth is to occur or even if normal health is to be preserved. The classical experiment by which Hopkins established the existence of vitamins was as follows.—He found that eight young male rats when fed on a purely synthetic diet, which was apparently complete with regard to carbohydrates, proteins and salts, did not grow at all. On adding fresh milk to the diet, growth immediately began and proceeded in a normal fashion. When milk was removed, growth stopped. From these effects, Hopkins pointed out that certain 'accessory food factors' are also needed for growth. For some years after the discovery of these substances by Hopkins, there was a tendency to regard them as highly unstable in character and to doubt whether they would ever be isolated or their chemical nature revealed. The outlook has profoundly altered in recent years. To-day, three of the vitamins have been isolated in very nearly the pure condition, and it is generally accepted that all members of the

class are substances of comparatively simple chemical constitution. Funk proposed the name 'vitamine' for these substances, as he thought that chemically they are of the nature of amines. The name 'vitamin' has now come to stay though it is spelt without an 'e.' Some of the American writers have still kept the original spelling, 'vitamine' employed by Funk.

Sources. The 'vitamins' or 'accessory food factors' occur in a great variety of foods, but appear to be formed mainly in plants. They are rather unstable and for the most part are stored in animals only, for short periods. Vitamins are present in most of the natural foods both animal and vegetable; particularly in glandular organs and products, including milk, eggs and liver and in green vegetables and fruits and in the embryo and hulls of cereals. They may also be prepared from yeast. Meats, potatoes, flour, most oils and sugar products are relatively deficient in vitamins.

General results of vitamin deficiency. The effects of vitamin deficiency resemble closely those of starvation. Growing animals, because of their relatively greater need of food, suffer more than adults and proliferating tissues suffer more than those that are stationary. Inadequate supply of the vitamins results in impairment of appetite, nutrition, growth, fertility, general health and of resistance to infective and other unfavourable agencies. Vitamin deficiency is probably also responsible for intestinal paresis and consequent stasis and bacterial fermentation. This observation gains support from the experiments of McCarrison. He found in pigeon and guinea pigs, suffering from experimental vitamin deficiencies that the intestine showed atrophy of the muscular coats, lesions of the neuro-muscular system and impaired digestion and absorption.

It is not always necessary that vitamin deficiency will manifest itself as in cases of frank disease like rickets, beri-beri, pellagra, etc. McCarrison and others have insisted that there are many cases of ill-health which are due to shortage of vitamins in the diet. Diarrhoea and gastro-intestinal complaints of obscure origin and lowered resistance to disease are believed to be associated, in many cases, with vitamin deficiency.

Classification of the vitamins. All the vitamins have not yet been isolated in a pure condition and, hence, it is not possible to offer a dogmatic classification. According to their actions and solubility they may be arranged into a few groups but it is not definitely known whether each group includes one or several substances. The existence of six different vitamins has now been fairly well established, and we will confine our remarks to these better-known factors to the exclusion of those which are still in an experimental stage. These may be classified as follows:—

Fat-soluble vitamins.

A—Anti-infective and anti-ophthalmic vitamin.

D—Anti-rachitic vitamin.

E—Anti-sterility or reproductive vitamin (vitamin X).

Water-soluble vitamins.

B—Anti-neuritic vitamin (vitamin F in U. S. A. terminology).

B₂—Anti-pellagra vitamin or anti-dermatitis vitamin (vitamin G in U. S. A. terminology).

C—Anti-scorbutic vitamin.

There are probably many other substances of this class which are not at present identified. There is, for example, 'bios,' a substance which appears to be essential for the growth of yeasts and bacteria and which bears some close relationship to B₁ and B₂. Before 1918, three vitamins, namely, A, B and C were only recognised. Vitamin A was recognised as a fat-soluble-vitamin, B as water soluble and C as anti-scorbutic. Later, vitamin A was split into A and D, A being anti-infective and anti-ophthalmic and D, anti-rachitic. Within the last few years, the existence of a third fat soluble vitamin E (or vitamin X) called anti-sterility vitamin, has been established. Vitamin B has been split into at least four components, of which two, B₁ or vitamin F and B₂, the so-called 'Pellagra preventive' (PP) or vitamin G, are here considered. There are probably many more similar substances. It is not really surprising that there should be a considerable number of substances which the animal

body requires in small quantities for growth and which it cannot manufacture itself.

Nature and properties of the vitamins. Ten years ago nothing was known regarding the chemical nature of these vitamins. To-day, it is possible to manufacture one of them, for vitamin D can be made by irradiation of ergosterol by ultra-violet light. Ergosterol can be obtained from yeast, and therefore this vitamin can be produced in a nearly pure condition in large quantities. Though we have got much less precise information with respect to the other vitamins, they can now be obtained in very concentrated forms which is a distinct advantage from the point of view of therapeutic administration. Concentrated A can be obtained from liver oils, and the provitamin 'carotene' from the yellow pigment of carrots, concentrates of vitamin B from yeasts and concentrates of vitamin C from orange juice. The medical use of vitamins is, therefore, practicable to-day.

An essential characteristic of some vitamins is that they are readily destructible. In nature, most of them slowly oxidise when food is preserved, unless oxygen is excluded. In most cases they are readily destroyed by alkali in the presence of oxygen or by absorbents (*e.g.*, charcoal) in the presence of oxygen. Hence great care should be taken to preserve them. No chemical tests are known by which most of the vitamins can be estimated quantitatively, and hence biological tests, which take a long time, are essential. There is a reaction by which vitamin A can be recognised but in the case of the other vitamins, biological methods have to be resorted to. Experience has shown that certain animals are highly sensitive to lack of certain vitamins and these animals are utilised in actual practice for purposes of testing and assay.

The quantity of vitamins required to maintain the body in health is probably a small fraction of a milligram a day. This suggests that they are more likely to be needed for the production of the hormones than directly for the general growth and nutrition of body cells.

Effect of cooking. Vitamins A, B, and D are fairly stable to heat and are not destroyed to any great extent in cooking unless alkali is added, as in cooking of vegetables. Eighty per

cent. of vitamin C content of vegetables is destroyed by boiling for an hour. Cooked foods may thus furnish an adequate supply for most of the vitamins except vitamin C.

The preservation of vitamin. Fat soluble vitamins can be kept active for years in solution in fats or in oils, especially if kept hermetically sealed. Tinned meat and butter may, therefore, contain these vitamins in adequate quantities. Vitamin B can be preserved for very long time in dried seeds and is only destroyed by some artificial process. Vitamin C can be preserved with great difficulty. The process of drying and preservation in tins completely destroy this vitamin in vegetables; but the vitamin C of fruits is more stable and can be preserved in the juices of citrus fruits and in tomatoes. Preservation of vitamin in milk is of a great practical importance in the feeding of infants. Pasteurisation and scalding of milk destroys about half the vitamin C content, whereas condensing or drying destroy only variable amount. Spray drying destroys the greater part of vitamin C; even by the best methods of drying about one half of the content of vitamin C can be retained.

Fate of the vitamins in the body. Little is known of the fate of the vitamins after ingestion; but they appear to be partly destroyed in the body and partly eliminated in the excrements. There is evidence to show that these substances are liable to be neutralised by the action of certain abnormal ferments or bacterial toxins in the alimentary canal, so that it may be necessary at times to give larger doses than those which ordinarily suffice

FAT SOLUBLE VITAMINS

Vitamin A

Occurrence. This factor is most abundant in animal tissues, particularly in the intracellular fat of liver and glandular organs and, therefore, in butter fat, egg-yolk, fat-fish, fish-roes, fish liver and cod-liver oil. It is also widely distributed in plants, especially in the green leaves. The A vitamin is apparently synthesised only by the chlorophyll of plants in the presence of light. Flower plants without any chlorophyll cannot produce vitamin A. Germinating seeds do not contain it until they have produced green leaves. Animals derive their supply of vitamin A from

the green plants directly or indirectly and store any excess especially in their livers and fatty tissues. The vitamin A content of foodstuffs of animal origin (milk, butter, eggs, etc.), therefore, is governed by the diet of the animal.

The original source of the fat-soluble vitamins in cod-liver oil is the chlorophyll-containing diatoms, which are eaten by plankton organisms and these, in their turn, by the small fishes which form the food of the cod. The fat-soluble vitamin in cod-liver oil have, therefore, passed through a series of animals before being stored in the cod's liver. Similarly the vitamin A in milk is derived from the fresh vegetables in the cow's diet and hence the milk of grass-fed animals is rich in this vitamin, but that of stall-fed animals may contain very little. In nature, vitamin A is always associated with the antirachitic vitamin D.

Carotene (provitamin). The yellow colour of many vegetables, especially carrots, sweet potatoes, yellow corn and certain vegetable oils, is due to a lipoid-soluble substance which has been isolated in a crystalline form by Schertz (1925) and later by von Euler (1928). This substance has been designated as 'carotene' and it has further been identified in animal kingdom, *e.g.*, in fish, hen's eggs, butter, corpus luteum, blood, etc., being derived probably from the food.

Euler showed in 1928 that carotene produced complete protection in animals on a vitamin A deficient diet. This statement was confirmed by Steenbock and his co-workers. The two substances, carotene and vitamin A, generally but not necessarily, occur in the same food-stuffs. Moore (1931) has reported that the feeding of animals with products rich in carotene greatly increased the vitamin A content of their liver fat, materially beyond that of cod-liver oil. It is, therefore, plausible to assume that carotene is biologically related to vitamin A and that carotene is a precursor of vitamin A and is converted into an active form in the body. The weight of modern opinion seems more to lean to the view that carotene is the precursor (the provitamin) inasmuch as it differs from vitamin A in certain physical, chemical and biological characteristics, *e.g.*, solubility, colour, absorption of light in the spectroscope and heat stability. The potency of active carotene approaches that of the vitamin A; 0.05 mg. produces normal growth in a 100 gm. animal which has been deprived of vitamin A. Carotene can be easily obtained and purified and has now been

accepted as an international standard for comparison of the vitamin A content of foods.

Composition and properties. The vitamin A is soluble in oil and fat solvents and also fairly soluble in water. It is less stable than vitamin D, being destroyed by oxidation. By passing oxygen through heated cod-liver oil, McCollum could destroy the A vitamin completely. In butter, the vitamin is confined to the portion of the fat with low melting point and is not destroyed by steam.

Steenbock succeeded in concentrating vitamin A into a fraction of the unsaponifiable lipoids of cod-liver oil. Seel (1930) claimed to have isolated the substance in a pure form which, however, was found to be very unstable. He believed that it is a labile oxidation product of oxycholesterol. Its relation with carotene has already been discussed.

Physiological effects. An adequate supply of vitamin A in the diet is essential for satisfactory growth in childhood and for the maintenance of a normal resistance against infection both in young and in adult life. Its deficiency causes suspended growth, increased susceptibility to infections and in advanced cases 'xerophthalmia.' The first symptoms of this trouble is night-blindness, a disease known for many years and fairly common in war prisoners' camps during the Great War. As the trouble progresses, opaque spots are seen on the sclerotic, then there is conjunctivitis and blepharitis and, if not checked, ulceration of the cornea, leading to blindness. Famine and industrial depression bring the disease to light. The experimental work of Mellanby and Green showed in a striking manner the lowering of the resistance against bacterial infection with a diet deficient in vitamin A. Clinically, this property of vitamin A has been utilised by many workers with very promising results. Lassen's work (1931) on the relation between vitamin deficiency and susceptibility to paratyphoid infection is very significant. In an extensive study he found that a decreased resistance to this type of infection was most noticeably associated with a reduced intake of vitamin A. The results of investigation on the role of vitamins A and D as

prophylactic agents against puerperal sepsis in the outpatient department of the ante-natal clinics of Sheffield are also very striking. Half the patients (out of 550 patients) were given an extra supply of vitamins during the latter week of pregnancy. Of these treated cases only 1.1 per cent. developed the British Medical Association standard of morbidity as compared with 4.7 per cent. in the control groups. Vitamin A deficiency is also supposed to be responsible for gingivitis, pyorrhoea, decay and an increased susceptibility to colds. These are, however, not definitely proved facts.

Deficiency phenomena in animals. 'Young animals respond promptly to vitamin A deficiency by arrested growth and xerophthalmia. In young rats, this may develop in 2 or 3 weeks. The epithelium of the eyeball and eyelids are not the only one to be affected. Animals kept on a diet without vitamin A show lesions of the epithelium of the mouth and throat, of the respiratory apparatus and of the urogenital tract. Von Veersum (1928) has shown that deficiency of vitamin A is one of the causes of stone formation in the kidney and bladder. Deficient bone formation is manifested by delayed dentition and rickets. In adults the results may not be noticeable for several months as they have got large reserves of vitamin A in their body fat. Body weight decreases and the resistance to infection is lowered. Intestinal disturbances occur and intestinal bacteria may invade the blood stream.

Colour (tintometric) test for vitamin A. When arsenic or antimony trichloride is added to an oil containing vitamin A, a blue colour is produced and the intensity of the colour is roughly proportional to the vitamin A content. This test provides a simple and rapid method for the approximate estimation of the vitamin A content of fats and oil and obviates the necessity for the biological test which requires 8-10 weeks. This colour test has not yet been established beyond all doubt as a measure of the vitamin A activity, but all the evidence so far obtained indicates that it is useful. The absorption spectrum of the colour produced in this test has been determined by Rosenheim and Drummond (1925) and confirmed by Wokes (1928). With arsenic trichloride bands at about 587 and 475 μ respectively were obtained. With antimony trichloride, bands at about 614 and 590 μ respectively were obtained.

Vitamin D (Calciferol)

This vitamin is present in cod-liver oil in relatively large quantities and also occurs in fish oils (*e.g.*, salmon, herrings in Western countries; *hilsa*, king fish, etc., in India), animal fats, eggs, and butter; green leaves contain only small quantities. It is now known that vitamin D is produced by the exposure of ergosterol to a special wave band of ultra-violet light. It may be produced artificially by such irradiation of the isolated ergosterol or of many foods and oils which contain ergosterol.

The history of discovery of vitamin D is particularly interesting. In 1922, McCollum, Simons and his co-workers showed that vitamin D is quite distinct from the growth-promoting vitamin A as the former is more resistant. Later work confirmed that 'D' does not protect against xerophthalmia and other manifestations of 'A' deficiency. In 1919, Huldshinsky noted that rickets could be cured by exposure to ultra-violet light and it was soon found that exposure to sunlight also exerted a powerful curative effect on rickets. This suggested that there was some connection between ultra-violet light and the fat-soluble vitamin. Hess and Steenbock (1924) independently and almost simultaneously discovered that antirachitic properties can be conferred on many foods and oils, which are not in themselves antirachitic, by short exposure to ultra-violet rays. Starting with the observation that ordinary cholesterol is rendered antirachitic by such irradiation, several investigators tried to discover what exactly was the molecular change that was brought about on irradiation. This led to the examination of many of the known compounds of cholesterol. After a good deal of experimental observations, it was found that cholesterol itself could not be turned into the antirachitic factor by irradiation but it was some impurity in that product. In 1926, Rosenheim and Windaus showed that the active principle or the provitamin D was indeed a sterol of an unsaturated and labile type, of which ergosterol is the only known representative. Ergosterol itself was found to have the same absorption spectrum as cholesterol which could be activated. The inevitable conclusion, therefore, was that ergosterol is the precursor of vitamin D.

Composition and properties. Ergosterol occurs in all tissues especially in the nervous system, skin and adrenals. It was originally produced from ergot and, therefore, called 'ergosterol' but is now prepared almost exclusively from yeast. It is chemically related to cholesterol but as has already been pointed out, differs from these sterols in its property of being activated by ultra-violet light and acquiring a property of curing rickets. The chemical nature of the change which takes place in the ergosterol following irradiation is not known. Possibly an isomeride of ergosterol is formed. That a good deal of change

occurs in the original molecule is revealed by successive alterations in the spectrum. During the early stages of irradiation of ergosterol, the amount of vitamin D slowly increases but a stage is reached at which formation and destruction go on at the same rate, so that for some hours the amount of vitamin D in a sample of ergosterol remains constant; then a stage comes when all the ergosterol has been converted into vitamin D, most of which has been destroyed. Continued irradiation completes the destruction of vitamin D and the preparation is without antirachitic property. The maximum amount of vitamin D present when a solution is irradiated at room temperature is about 10 per cent.

This work naturally suggested the advisability of irradiating ergosterol with rays of particular wave length only, and not with the whole range which comes from a mercury vapour lamp, some of which obviously have a destructive effect. Vitaglass cuts off the rays below 260 and would, therefore, apparently be useful in letting through the needed rays.

The antirachitic property of activated ergosterol or 'viosterol' is 250,000 times that of cod-liver oil and 0.00002 mg. would protect a rat against experimental rickets. The pure dry viosterol soon loses activity but irradiated foods remain active for at least six months and oily solutions of viosterol appear to retain their full activity indefinitely.

Effects produced by vitamin D. Deficiency of vitamin D in the diet results in deficient and defective formation of teeth and bones. The administration of viosterol cures the defective bone development and all other manifestations of human rickets and that produced in experimental animals by diets deficient in vitamin D. How this bone development is retarded is not known. There is evidence to suggest that one of the primary effects of vitamin D deficiency is to render the gut contents more alkaline than normal and thus to interfere with the absorption of calcium. The improvement after the administration of vitamin D starts with progressive calcification at the epiphyses, and is evidently connected with the proper relation of calcium and phosphate in the blood. Even when the diet contains the proper amounts of calcium and phosphorus which are necessary for bone formation and bone development, lack of vitamin D results in a disturbance of the metabolic balance resulting in defective bone formation. In the growing animal the bones laid down are so deficient in calcium phosphate that they are unable to support weight and bend.

The mechanism of action of vitamin D is unknown. It resembles at least superficially that of the parathyroid hormone but the effect is not exerted solely through this gland since it occurs also after parathyroidectomy, although the doses to be given must be a thousand times more than the ordinary.

Effect of overdosage. Attention has been called, during the past year or two, to the possibility of a disease or a condition caused by overdosage of vitamin D known as *hypervitaminosis*. A single dose, even if large, does not produce permanent ill effects but continued administration results in the depressive symptoms of hypercalcaemia. Loss of appetite, lassitude, drowsiness, pallor, emaciation, etc., are some of the signs noticed in these patients and later calcification of tissues, *e.g.*, arteries may take place. The susceptibility varies somewhat in different individuals but the margin between therapeutic and deleterious dose is a wide one.

Diseases Produced by Vitamin D Deficiency

Rickets. Rickets does not play so great a part in the tropics as in cold countries. According to an estimation by Hess, rickets occurs to the extent of nearly 7.5 per cent. amongst the children of the urban population of the temperate regions. This is certainly not the case in India and other tropical countries but the disease is not altogether unknown. There are some places in Southern and Western India where a mild form of rickets is fairly common among children, who are reared in dark rooms.

It is now definitely known that rickets is caused by deficiency of the antirachitic vitamin. For many years, there was a dispute as to whether rickets was caused by a deficient diet or by bad housing and consequently deficiency of sunlight. Recent experiments have explained the results satisfactorily and have shown that when an animal is exposed to sunlight or to the ultra-violet light from a mercury vapour lamp, a certain amount of vitamin D is synthesised in his skin. Hence rickets can be prevented or cured either by the supply of an adequate amount of vitamin D in the food or by exposure of the subject to ultra-violet light or sunlight. Cod-liver oil, fresh milk

animal fats, butter, etc., contain fairly high percentage of vitamin D and can be used in all such conditions. Irradiated ergosterol or viosterol is a highly concentrated form of vitamin D and can be used when cod-liver oil cannot be tolerated on account of gastro-intestinal disturbances. In tetany and spasmodophilia and during the lactation period, vitamin D is also of great use.

Osteomalacia. This disease is very common among females in some towns and cities in India (Bombay) and Kashmir and also in other countries in which the purdah system prevails. It is entirely unknown among people who lead an outdoor life. There is abundant evidence that the disease is caused by lack of sunlight and antirachitic vitamins. Osteomalacia has frequently been called "adult rickets."

The disease may occur in a very mild form among males but it is essentially a disease of women who are forced to live in purdah in many parts of India. The disease makes its appearance particularly at the time of attainment of puberty and is frequently exaggerated at the time of pregnancy when the foetus takes away much of calcium from the mother's blood. Manifestations of hypocalcaemia become evident in the form of general weakness, pains in the pelvic regions (so-called 'girdle pains') and tetany and spasms of the muscles. In due course, softening and deformity of the bones set in. These cause their most disastrous effects in the pelvic bones—the bony pelvic outlet is shortened and there is great difficulty at the time of parturition.

The administration of vitamin D either through food or as irradiated ergosterol has prevented the progress of the disease; in many cases sunlight and fresh air to stimulate the skin to manufacture vitamin D should also be resorted to. Viosterol is, however, not so specifically active in this disease as it is in rickets.

Dental caries. What is true of bones is true also of teeth. Deficiency of vitamin D in puppies, rats and rabbits, has produced a condition of caries which is very similar to that affecting human teeth. For teeth to be perfectly formed a supply of vitamin D from the inception of calcification till it

is complete, is therefore essential. Moreover, the production of well calcified secondary dentine, so useful in protecting the pulp cavity from the effects of attrition or of caries, also demands an adequate supply of vitamin D. Already it has been shown that the supply of vitamin D to children arrests the rate of progress of caries. It is therefore likely that the major findings in connection with dental decay, observed in experimental animals, are true in man.

Vitamin E or X (Antisterility vitamin)

Evans found that rats could be reared on a synthetic diet plus the usual vitamins and might grow normally and appear perfectly normal but yet be unable to reproduce. When such food was given to females, ovulation and impregnation occurred but the implanted foetus died. With males, the germ cells are injured to partial or complete sterility. The degeneration of the testis brought about by a continued lack of it is irrecoverable but in the case of the female, recovery from this shortage seems to be possible even in the most advanced stages.

Occurrence and properties. Vitamin E is a fat-soluble vitamin occurring in most natural foodstuffs like cereals, green leaves, etc., and in particularly high concentration in lettuce, bemax and wheat germ. It is a constituent of the unsaponifiable matter of wheat germ oil, is not destroyed by acetylation, is heat stable, and in strong contrast to vitamin A is not easily oxidised. It is stored in the animal body so that a temporary shortage would not have much effect.

Evans' latest work shows that this vitamin is also growth-promoting to a certain extent. It is also believed to have a lactation-promoting element as well but this has not received much support.

The efficacy of vitamin E extract has thus far been found useful only in rats. No definite proof yet exists that it will play the same part in human mechanism. There appears to be no likelihood that a shortage of vitamin E is of importance in human nutrition. None the less, claims have been made that it is of value in the treatment of sterility.

WATER-SOLUBLE VITAMINS

Plants of all kinds and certain animal products like milk, eggs, liver, etc., contain water-soluble substances which promote nutrition. Diets that are deficient in these lead to arrest of growth, loss of appetite and of weight, anæmia, nervous and circulatory disturbances, skin lesions and progressive inanition which terminates in death by starvation. The phenomena are promptly corrected when food or extracts containing the B vitamins are added to the diet. These events are in reality complex resultants of the deficiency of soluble substances which generally occur together in nature and which were, therefore, originally considered as one entity and designated as 'vitamin B.' It is just about 5 years since various workers on vitamin B began to obtain definite information on the dual nature of vitamin B. Hassan and Drummond (1927) in an attempt to discover what it was that counteracted the ill effects of high protein diets, discovered that not only yeast itself could do this, a fact which had been demonstrated by various workers already, but also that yeast autoclaved in an alkaline medium could do it. This treatment was known to inactivate the factor generally known as vitamin B, that is the factor that can cure polyneuritis in pigeons. Seidell, and later Chick and Roscoe (1927) added further evidence on the dual nature of vitamin B and it is now generally accepted that what used to be called vitamin B, really consists of at least 2 factors. (Hence termed 'vitamin B' complex). These have been named B₁, the antineuritic and B₂, the anti-pellagra vitamin. Both B₁ and B₂ are necessary for growth and both these factors occur in association in nature.

Further evidence is gradually growing that in addition to the two water-soluble vitamins already described there is another vitamin or perhaps rather a group of vitamins (provisionally termed B₃, B₄, B₅), which promote growth without being antineuritic or pellagra-preventing. Lately, it has been very definitely proved that a very large excess of both B₁ and B₂ will not bring about normal growth. It is unnecessary

to postulate, at the present stage of our knowledge, the existence of other factors.

The Antineuritic Vitamin B₁ (F)

Deficiency of this vitamin causes arrest of growth in young animals, and produces polyneuritis in adults. Birds are particularly susceptible to the lack of this vitamin and pigeons develop polyneuritis within 20 days when fed on a vitamin B-free diet. Rats on a hulled rice diet die from inanition with relatively little anaemia and no polyneuritis. Deficiency of B₁ factor causes atrophy of the mucous membrane and muscular coats of the bowel. There is also evidence of atrophy of the lymphoid tissue including Peyer's patches in the intestine of the rats. It will thus be seen that different animals require different periods to develop the disease and the manifestations are slightly different though the pathological basis remains the same in all animals.

The phenomena disappear promptly and completely if foods or extracts containing the antineuritic vitamin are administered early. If they are delayed until the degenerative changes of inanition, particularly the neuritis, are too far advanced, the progress is merely delayed and the decline proceeds to death.

Nature and properties of vitamin B₁. This is water soluble and dialysable. It is insoluble in ether or absolute alcohol but dissolves in ordinary alcohol, especially if this is acidulated. It is readily adsorbed on Fuller's earth and charcoal and may possess a tertiary amine group.

This vitamin is highly resistant towards acids, remaining unaltered on boiling for twenty-four hours with 20 per cent. mineral acids. Alkalies do not destroy it at room temperature. It tolerates heating to 100°C. for several hours in neutral and acid solutions. It is, however, quickly destroyed when heated to 120°C. This property is made use of in separating the antineuritic from the antipellagra factor. Autoclaving yeast at 120°C. destroys the B₁ factor while B₂ factor practically remains unaltered.

Highly active concentrates have been obtained of B₁ vitamin by special adsorbents and differential solvents. Peter's extract from yeast protects pigeons in dosage of 0.084 mg. per day. A crystalline substance from rice, isolated by two Dutch scientists, Jansen and Donath, protects pigeons with 0.08 mg. dosage per day. A chemical

formula has also been ascribed to this crystalline substance. Recently, much more active extracts have been obtained by other workers.

Levene (1928) has shown that pure B_1 vitamin can be obtained by deaminising yeast. Deamination kills vitamin B_2 whereas B_1 remains unaffected. This observation has, however, been contradicted by other workers.

Vitamin B_1 Deficiency Disease

Beri-beri. There is a good deal of difference of opinion as to the true etiology of human beri-beri. Many workers have adduced cogent arguments to show that human beri-beri differs strikingly from the avitaminosis which is produced experimentally in birds (polyneuritis gallinarum); in beri-beri there is oedema, cardiac excitation and hypertrophy, whereas in avian avitaminosis, there is drying up of the tissues and cardiac atrophy. Another important point of difference is that in many outbreaks of human beri-beri there has been no evidence whatever of a previous shortage of vitamin B in the diets of the patients. Other arguments against acceptance of the vitamin deficiency view are that the manifestations of the disease are those of a toxic neuritis rather than of a food deficiency and the outbreaks are sometimes of an explosive nature, such as could hardly occur if we were dealing with a food deficiency. The seasonal distribution also suggests the formation of a poison in the rice during hot and damp weather. The theory, therefore, that human beri-beri is essentially caused by a food intoxication rather than a food deficiency is gradually gaining ground. Whatever be the essential cause of the common form of beri-beri, it is probable that deficiency of vitamin B_1 in the diet is a predisposing factor.

Vitamin B_1 may be supplied through many articles of diet. Rice hulls or their water or alcoholic extract ('tiki tiki'), the hulls and the embryo of other grains and yeast are all rich stores of this vitamin and when administered early in the course of the disease produce very satisfactory results and may arrest the progress of the disease in many instances. As beri-beri is essentially a disease of the rice-eating countries and as rice is considered also to be a source of infection, complete stoppage of rice in the diet is recommended to be a safe course.

Vitamin B deficiency. McCarrison showed that partial deficiency of vitamin B caused marked wasting in the gastrointestinal tract; Plimmer confirmed this and showed that partial deficiency of vitamin B continued over several months in birds did not cause polyneuritis, but affected the intestine profoundly. The chief effects were atony of the gut, with consequent constipation and stasis, distension of the bowel and auto-intoxication.

Plimmer found that although a very small quantity of vitamin B was sufficient to prevent polyneuritis in birds, yet a considerable supply was needed to maintain them in full health. He also found that the amount of vitamin needed was proportional to the amount of food supplied, and that a quantity of vitamin which was sufficient to maintain a bird in health on a spare diet, became insufficient if the diet was increased by the addition of vitamin-free food. Excess of carbohydrate, in particular, increased the need for vitamin B. In the tropics, particularly in India, where carbohydrate foods are consumed in excess, the need for vitamin B is much more pronounced than in colder climates. The wide prevalence of gastro-intestinal disorders in India may have some relation with vitamin B deficiency. Diet in the tropics should, therefore, be regulated in such a way that vitamin B is supplied in excess of the normal demands. Unless this is done, the body metabolism may fail whenever an extra strain is thrown on the system, *e.g.*, during the time of pregnancy and lactation in women and at the time of active growth in young men.

Anti-pellagra Vitamin, B₃ or G or (PP)

If young rats are kept on certain limited diets such as oats, a train of symptoms appear within 3 to 4 weeks, which are quite characteristic. The growth is markedly interfered with, inflammation and ulceration of the buccal mucous membrane sometimes going on to sloughing, dermatitis and nervous lesion are also noticed. Chittenden and Underhill (1917), and Chick and Hume (1920) obtained the same train of symptoms in dogs and monkeys respectively. The lesions resemble those of human pellagra, a disease characterised by a dermatitis of

exposed surfaces, first described by Casal in Spain. Goldberger and Little (1926) found that the experimental pellagra-like disease produced in animals could be cured by the administration of yeast which was previously heated to 120°C. at 15 pounds pressure to destroy its antineuritic properties. The factor responsible for this was named the pellagra-preventing (PP) vitamin. The experimental work has been confirmed and extended by Chick, Hume and other workers.

Pellagra occurs chiefly in maize-eating countries, particularly in Italy, Spain, Roumania and the corn-fields of the Southern States of North America. Rare isolated cases occur in England, India and other countries but most of these have been shown to be associated with the eating of maize in the form of cornflour.

A great variety of theories have been advanced to account for this disease but the position is much the same as in connection with beri-beri. Goldberger and others believe the disease is due to the deficiency of vitamin B₃ (PP or G) but there is another school who do not agree to this view. There are reasons for believing that the composition of the protein of the diet may be a factor of equal importance to the vitamin B₃ content. Probably the vitamin deficiency factor is not the sole causative agent. There is a definite association of the disease with a special food grain so that a positive toxic factor would be more likely to occur than an absence of some nutritive property. However, it is certain that this vitamin is an essential dietary unit for growth and normal health and that it is an important factor in the treatment of pellagra.

Properties. This vitamin has not been isolated. It is soluble in alcohol, in water and is thermostable to a much greater extent than its colleague. Levene (1928) has found that silica gel has the power of absorbing both B₁ and B₃, but it absorbs B₃ preferentially. This observation can be utilised in obtaining an yeast extract which is much more active in its B₃ content. Ordinary dried yeast contains both B₁ and B₃ in the proportion of 1 : 7.5 and the material obtained from the silica gel contains them in the proportion of 1 : 30.

Anti-scorbutic Vitamin C

Occurrence. This vitamin occurs in all growing vegetable tissues. Green vegetables, fresh fruits (lemons, oranges, tomatoes, etc.), potatoes, onions, etc., contain large quantities of this vitamin and smaller quantities are contained in fresh meat and milk. This vitamin has been definitely proved to be a protective against scurvy.

Properties. Vitamin C is very unstable and is destroyed on cooking or drying. It is, however, fairly stable in the rind of citrus fruits and in tomato juice. Ordinary cooking destroys most of the vitamin C in vegetables and the duration of the heating is more important than the temperature to which they are raised. Cabbage loses about 80 per cent. of its vitamin C content by heating to 100°C. for twenty minutes or by heating to 60°C. for an hour. The vitamin of the citrus fruit and tomato is stable even on cooking. This is perhaps due to the protective action of the acid.

A curious fact, and one which has, on more than one occasion, been put to practical use, is that the vitamin C is completely absent from dried grain but is formed during germination. A supply of vitamin C can therefore be obtained by allowing grain or peas to germinate. The body cannot store vitamin C and depends for its supply upon fresh vegetables.

The chemical nature of vitamin C is not known. Recently, Szent-gyorgyi (1933) has isolated a substance named ascorbic acid (originally named hexuronic acid) which is claimed to be identical with vitamin C. This vitamin is water soluble and dialysable. Zilva (1927) has prepared concentrated anti-scorbutic vitamin from lemon juice, and with this preparation, very good results can be obtained in clinical scurvy.

Vitamin C may shortly be shown to consist of two factors, one anti-scorbutic and the other growth-promoting. These have however not yet been definitely established.

Effects due to lack of vitamin C. The chief symptoms of scurvy are sore and bleeding gums, diarrhoea, cedema and haemorrhages which may occur in any part of the body. Weakness is also a prominent feature. The disease was very common

in sailors in the days of long-sailing voyages and Polar expedition. Scurvy in adults is rarely encountered at the present time. Severe outbreaks were observed in Murmansk in 1919, and in the famine areas of Russia in 1922, but in Western Europe and America, it is almost unknown. The children are more commonly affected due to improper feeding and hence infantile scurvy is commoner. Barlow's disease occasionally seen to-day in infants is probably due to lack of vitamin C. This is also fast disappearing owing to the general recognition of the value of fruit juice in supplementing the possible deficiency of a milk diet. Most of the dietaries of the tropics are quite well supplied with anti-scorbutic substances and, therefore, scurvy is very seldom found in India. The susceptibility to scurvy varies widely for different kinds of animals. Guinea pigs develop typical scurvy after 3 weeks without green food. Human beings take a much longer time to develop the disease (120 days on an average). Rats, mice, cattle and fowl appear quite unsusceptible, apparently they are able to manufacture the vitamin in their liver.

Toxamins. Mellanby (1930) has proved the existence in the germ of cereals of substances which antagonise the fat soluble vitamins. The germs of oats contain more of these than does wheat germ, whilst ergot is particularly rich in toxamins. Ergot and germ of cereals can also produce sub-acute combined degeneration in the spinal cord, an effect that is prevented by an adequate supply of vitamin A.

The nature of toxamin is at present unknown.

Conclusion. A short account of vitamins from the standpoint of therapeutics is given. Vitamins are becoming popular everyday and vitamin preparations are coming into the market in increasingly large numbers. It must, however, be remembered that their role of utility is very limited in the tropics. So far no very acute symptoms of deficiency of vitamins A, D, C and E have been evident in this country. Epidemic dropsy is fairly prevalent in India but this also has been shown to be not definitely due to lack of vitamin B and the administration of active B extracts has not been able to prevent or cure the disease completely. The food in the tropics may be deficient in protein and other constituents but is certainly not lack-

TABLE SHOWING THE CHIEF FEATURES OF THE VITAMINS

Vitamins	Diseases caused by deficiency	Diets rich in vitamin	Special properties of vitamin	Medicinal preparations available and remarks.
Vitamin A. Soluble in fats & oils.	Xerophthalmia, night-blindness. Susceptibility to bacterial infections. Retardation of growth.	Cod-liver oil, fresh milk butter, fresh eggs, liver, fish roe, fish liver oils, fresh vegetables like carrots, spinach, tomatoes, cabbage, yellow maize, bicurus (alfalfa), green leaves, etc.	Heat stable at ordinary cooking, destroyed by boiling at 100°C. for 6 hours. Constitution not settled. The plant pigment carotene is closely related to it. Active crystalline preparations have been obtained.	'Avoleum' (B.D.H.) 'Haldol' (B.C.P.W.)
Vitamin B₁ or Vitamin G of Americans. Soluble in water.	Restricted growth, malnutrition, beriberi, digestive disorder, e.g., loss of appetite.	Brewer's yeast, legumes, cereal grains (unmilled), eggs, liver, fresh vegetables, milk, malt extract, etc.	Little affected by cooking, drying or preserving in tins. Destroyed by heating with alkalies, but stable in neutral or acid solution. Active crystalline preparations have been obtained.	Available in yeast preparations, 'Vity's' (B.C.P.W.)
Vitamin B₂ or Vitamin G₂ of Americans or Pellagra-preventing (P.P.). Soluble in water.	Loss of weight. Pellagra.	In nature usually associated with B ₁ ; yeast, legumes, etc.	More stable than vitamin B ₁ . Crystalline preparations have been obtained.	'Vity's' tablet (B.C.P.W.)
Vitamin C. Soluble in water.	Scurvy.	Lemon & orange juice, tomatoes, fresh vegetables, germinating leguminous seeds, fresh fruits, fresh milk, etc.,	Heat labile, very easily destroyed. Tomatoes & lemon juice sterilised by boiling retain vitamin activity.	'Ascorbic acid' is identical with vitamin C.
Vitamin D. Fat soluble.	Rickets, osteomalacia, dental decay, faulty absorption of lime and phosphates.	In nature always associated with vitamin A, cod-liver oil, irradiated ergosterol, germinating grains, fresh vegetables, butter and fresh milk, etc.	More stable than vitamin A. Unaffected by cooking. Irradiation converts ergosterol into vitamin D.	Irradiated Ergosterol in oil 'Vigantol,' 'Ostifin,' 'Rayneol,' etc. International unit adopted.
Vitamin E. Fat soluble.	Disturbances in gestation. Sterility, nonlactation.	Wheat embryo, egg yolk, fresh vegetables, liver, milk, etc.	Stable.	Obtainable in food products and in concentrated form in wheat germ oil.

ing in vitamin content. Green vegetables are available in plenty and form the daily ration of even the poorest member of the civil population. The Eastern habit of keeping their bodies exposed to the sun and the plenty of sunlight available are highly conducive to the abundant production of vitamin D from the ergosterol in the skin.

Although the vitamin content of the average dietary is generally adequate for the normal requirement of the population, there will always be a need for the use of extra supplies of vitamins either through natural sources or through vitamin preparations to meet periods of emergency such as pregnancy, lactation or for use in infancy and childhood when growth is rapid. A little excess of vitamins consumed through foods will not do any harm but may stand in very good stead when an extra demand arises. It should be realised, however, that the amount of vitamins required to preserve normal health is very small, probably only a small fraction of a milligram a day for an adult and most of the dietaries in different countries contain ample quantities for this purpose. Large quantities of vitamins supplied in form of proprietary preparations may do more harm than good.

Preparations.

Liquor ergosterolis irradiati. B. P. is a solution in oil of an antirachitic principle. It contains 3,000 units of antirachitic activity per gramme. It should be kept in a well-closed container, protected from light and stored in a cool place. The prophylactic dose for infants is 5 to 15 minims daily (1,000 to 3,000 units) and the curative dose for infants is 25 to 50 minims daily (5,000 to 10,000 units).

Radiostoleum. It is a solution of vitamin A concentrate and radiostol (irradiated ergosterol containing vitamin D) in a vegetable oil. It is standardised to contain 3,000 international units of antirachitic activity per gramme; it is doubly standardised as to its vitamin A content. It is stated to have 30 times the vitamin D and 60 times the vitamin A activity of high grade cod-liver oil. It is administered orally in doses, of half to one tablespoonful daily.

Vleosterol in oil 250 D. Irradiated ergosterol is dissolved in a vegetable oil and standardised to contain 3,333 rat units of vitamin D in each gramme, the strength being 250 times that of a potent cod-liver used. The average prophylactic dose for infants and children is 8 to 10 drops (0.1233 to 0.1666 c.cm.) in severe cases and for adults, doses in

excess of 20 drops may be given. There are various other preparations in the market (Abott's, Mead's, Parke Davis & Co.'s, Squibbles' and Winthrop's.)

Oscodal. It contains in each gramme not less than 25,000 vitamin A units (U.S.P.) and has a vitamin D content such that 0.075 mgm. per day will suffice to initiate recalcification in the leg bones of young rachitic albino rats in 10 days. For infants and children the usual dose is from 0.01 to 0.04 gm. and for adults from 0.04 to 0.06 gm. three times a day.

Haliverol. It is the oil obtained from halibut livers, to which irradiated ergosterol is added in such proportions as to make its vitamin D potency equal to 250 times that of high grade cod-liver oil. Its vitamin A potency is 60 times that of high grade cod-liver oil. The average dose is 8 to 10 drops daily for infants, for premature and rapidly growing infants 15 drops daily and for adults especially nursing expectant mother's 20 drops or more daily.

Adexolin. It is a concentrated solution of vitamin A and D. It is supplied in capsules, each containing 3 minims, the usual dose is 2 to 3 capsules twice a day.

Bemax. It is a cereal preparation made from wheat, ryes, or barley. It is stated to contain a greater proportion of vitamins B₁, B₂, and B₆ than any other product of its kind. It is also rich in E and A. The dose is one tablespoonful daily.

Metagen. It is a combination of water soluble and fat soluble vitamins in extract form and physiologically tested. It is supplied in capsules; the usual dose is 1 to 2 capsules, three times daily, before meals (P. D. & Co.).

Marmite. It is a palatable yeast extract rich in vitamin B. One to two teaspoonfuls twice a day is the usual dose which can be added in soups, etc.

Vitamin contents of different articles of food will be found in the Appendix.

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CHAPTER VIII

PYREXIA

The normal body temperature. The human body is adjusted to work best at a certain temperature, which is called the normal. Any variations from it are detrimental to the proper working of the organism. Provision is therefore made in the body to regulate the temperature and keep it at the required level. In the cold-blooded or poikilothermic animals, the temperature depends on the surroundings. It rises in hot weather and falls in the cold and the life of the animal varies accordingly. In the warm-blooded or homo-thermic animals, the temperature is maintained at a constant level independently of their surroundings. Transitional forms between these two types occur such as in hibernating animals. The mean body temperature maintained by warm-blooded animals differs in different animals, *e.g.*, among the birds it usually lies between 40°C . (104°F .) to 43°C . (107.6°F .) or more. In most mammals, the mean body temperature is lower than birds' but somewhat higher than that of man.

Normal variations also occur in the body temperature in human beings. The normal temperature in man is usually taken to be 37°C . or 98.4°F . but it is well known that the temperature differs in different parts of the body and also at different times of the day. The rectal temperature is nearly 0.6°C . or 1.0°F . higher than the mouth temperature; the temperature in the axilla is 0.6°C . or 1.0°F . lower than the mouth temperature. As regards the diurnal variations, the temperature rises during the day and attains its maximum late in the afternoon (37.5°C . at 6 p.m.); it falls during the night and reaches its minimum in the early hours of the morning (36.2°C . at 4 a.m.). The difference in the maximal and minimal temperature usually amounts to somewhat over 1.0°C . or 1.7°F . The cause of these variations is not clearly understood, but is attributed by some to muscular activities during the day and rest during the night. Food has also something to do with it, as diurnal variations of temperature are not so marked during

starvation. The temperature also varies at different periods of life. The temperature in the infant is higher than in later life.

Regulation of body temperature. Apart from the small diurnal variations, the temperature of the body is maintained at a remarkably constant level by the physiological processes in the body. This is accomplished by a fine adjustment of heat production and heat loss. Any change in the environment which involves a marked increase or decrease of temperature quickly brings the heat-regulating mechanism into action. The temperature of a normal person rises when muscular work is undertaken. A brisk walk for two hours may raise the rectal temperature of a healthy person from 37.0°C . to 38.4°C . (101°F .). In certain diseases such as tuberculosis the diurnal variations as well as the rise of temperature produced by exercise is increased. The brain can only function normally within a narrow range of temperature. A fall of 3°C . below normal produces narcosis, whilst a rise of more than 4°C . above normal may produce delirium.

Heat production is governed by : (1) The motor nerve centres and motor nerves to muscles and glands. (2) The quantity and quality of the food consumed. The heat generated depends on the amount of food oxidised and the activity of glands and muscles. Thus a starving animal shows a lower temperature than one fed normally. Although muscular activity plays a very important part in the production of heat, it has been shown that even if the voluntary muscles are paralysed by administration of curare, a high temperature can still be maintained in febrile animals. The production of heat in these cases must apparently be due to the activity of glands and involuntary muscles. Metabolism and the body activity of the voluntary and involuntary muscles and of the glands are, therefore, important factors in the production of heat.

The heat produced depends upon the basal body metabolism and upon excesses above this resulting from muscular activity and the ingestion of food. The basal metabolic rate (B. M. R.) of an individual means the production of heat with the body at complete muscular repose and fasting. The rate is subject to marked physiological fluctuation. According to Benedict the

average basal metabolism of a normal adult is about 25 calories per kilo. of body weight per day. The B. M. R. is usually calculated in calories per sq. meter of body surface. If height and weight of an individual are known, his body surface can be calculated from tables. The normal B. M. R. is 40 calories per sq. meter of body surface per hour. Lighter individuals though showing a smaller total metabolism than heavier ones, usually have a greater metabolism per unit of body weight. The heat production is increased by exercise, by food and exposure to cold. A normal man of sedentary habit produces about 3,000 calories a day, while a manual labourer produces as much as 6,000 calories per day.

The heat is lost mainly through, (i) radiation and conduction from the skin, (ii) evaporation of water from the skin and respiratory tract. Heat is lost also through the excretions, in the process of warming the inhaled air and the ingested food taken at a lower temperature. In temperate climates, approximately 75 per cent. of heat is lost by conduction and radiation if a man is doing some physical work. During rest, heat loss through evaporation comes more prominently into play. If the heat loss is suddenly increased by the application of cold to the surface, there will be a reaction on the part of the body resulting in constriction of the peripheral blood vessels and shivering. The constriction of blood vessels is brought about by the vaso-motor centre in the medulla which ensures that the blood supplied to the vital organs is maintained at a proper temperature. The constriction will lessen the amount of blood circulating through the skin vessels and thus reduce the heat loss through the skin. Shivering will increase heat production and by diminishing heat loss and increased heat production the effects of sudden cooling will be counteracted. Increase in the surrounding temperature will, on the other hand, involve the reverse kind of reaction by the same heat-regulating mechanism. There will be a dilatation of the skin vessels and increased perspiration. Both these factors will prevent the body temperature from rising above the normal, by increasing the heat loss from the body. The temperature is thus kept constant by changes in the production and dissipation of heat.

The delicate adjustment of heat production and heat elimination is under the control of the central nervous system. The principal centres concerned in heat regulation lie near the basal ganglia and control both the production and the dissipation of heat. They in their turn are influenced by afferent stimuli from the skin and mucous membranes as well as by the temperature of the blood which circulates through them, and they work in close co-operation with the vasomotor respiratory and the sweat centres. Sensitiveness of the heat centre was shown by Barbour to be extremely delicate. By heating or cooling the blood going to the centre, he showed that slight changes in the temperature evoked a compensatory response.

Regulation against over-heating. If the amount of heat generated is greater than that eliminated, a rise of body temperature is the result. Production of heat is increased after food and especially after protein food, but this increase is never great and is promptly eliminated. Over-eating especially by consumption of meats may increase discomfort during hot weather by throwing an extra burden upon heat elimination, but this rarely causes any appreciable rise. Muscular activity, on the other hand, is one of the important causes of over-heating. It has been seen that during moderate exercise the total metabolism of the body may be increased 2 to 3 times and after violent exercise 5 to 8 times the normal resting metabolism. With the increase in metabolism, the temperature of the body rises and it is quite common to see an increase of 2° to 3°F. in the rectal temperature. An equilibrium is, however, maintained by increased dissipation, by radiation, conduction, evaporation from the surface of the body and by deep breathing. When this elimination is defective, a serious rise of temperature may occur and heat stroke may result. This phenomenon is very well illustrated in the case of certain animals like the dog in which perspiration is almost absent. If evaporation from the tongue is prevented in such an animal, by making him breathe through a tracheotomy cannula and the animal is made to take exercise, the temperature rises so high, following a brief period of muscular exercise, that the animal may die of heat stroke. In man, in certain diseases of the

skin, *e.g.*, ichthyosis, the power of dissipation of heat through the skin is interfered with and in these patients muscular exercise may produce an unusual rise of temperature. If the external temperature is higher than that of the body, the heat loss is not carried out by conduction but by evaporation of sweat, which is secreted to a greater extent on account of an increased flow of blood in the cutaneous vessels. In man this is the chief means of regulation of temperature if the surrounding temperature is high. The nerve centres are guided in this regulation, (1) by the temperature of the blood coming to them and (2) by reflexes from the skin. If in experimental animals the temperature of the blood going to the centres is raised, the various changes that characterise regulation against over-heating come into force. In man reflexes from the skin play a very important part. The rate of evaporation depends on the humidity of air. Movements of the air assist in evaporation from the skin and excessive heat is borne better when the air is in motion. In tropical climates, where the external temperature is high, the increased dissipation keeps the temperature down, at the same time the individual feels relaxed, restricts his exercise and food and thus helps in diminishing heat production.

Regulation against over-cooling. Man can tolerate a much greater range of low temperature, protection against heat loss being assisted by a thick layer of fat under the skin which is a bad conductor of heat. In animals, fur and other covering, and in man clothes prevent dissipation. Besides this, two other factors are important: (1) Physical regulation, *i.e.*, by constriction of cutaneous vessels so that less blood flows through the periphery. Even exposure to moderate cold reduces the cutaneous supply of blood of the arm to one-half or less of what it is at a comfortable temperature. (2) Chemical regulation, *i.e.*, by increased metabolism in the muscles as shown by shivering. This only comes into force when the physical regulation does not suffice. After division of the dorsal cord the metabolism fails to show the characteristic change when the animal is exposed to cold, because of the paralysis of muscles. Extra heat is also obtained by ingestion of food. As in the case

of over-heating, the mechanism is under the control of nerve centres which are influenced by sensory impulses from the skin. If the skin is suddenly cooled a reflex constriction of the cutaneous vessels of the body occurs immediately. A cold bath often causes a rise of temperature by increased muscular activity by shivering and constriction of skin vessels.

PYREXIA AND ITS TREATMENT

Conception of fever. Fever is derived from Latin word *febris* meaning to boil. It is a complex phenomenon, the main feature of which is a rise of the body temperature associated with disturbance of metabolism, special senses, pulse, respiration, etc. The rise in temperature in fever is due to a defect in the heat regulating mechanism, which is not clearly understood. Physiological fever, we have already seen, is produced by immersion in a warm bath at 40°C. and is not accompanied by any of the other phenomena of fever above described. Entrance of living or dead bacteria or their products in the blood or protozoal organisms produces fever. No constant relation exists between the severity of infection and the height of fever. The cause of marked fluctuations in temperature during infections is not understood. In some it is merely an exaggeration of normal diurnal variations. Other conditions giving rise to fever are injection of foreign proteins, destruction of cells in the body in the absence of bacteria (*e.g., extravasated blood*) and a number of chemical poisons. The injection of certain salts, sugar, sulphur, atropine, caffeine, cocaine, strychnine, picrotoxin, tetrahydro-beta-naphthyl-amine, epinephrin, and many other substances will increase the temperature when given in large doses. Puncture of the brain in the region of the corpus striatum produces fever which is associated with constriction of the peripheral blood vessels and an increased production of heat within the body, mainly from combustion of carbohydrates derived from hepatic glycogen. In a general way the rise resembles that which occurs during infective processes; essential and undoubted differences have not been established between the two. The probable explanation is that the rise of temperature in infectious disease is due to stimulation of the heat regulation centres by some products of infection. Clinically, rise of temperature occurs after cerebral hæmorrhage, especially into the ventricles, due to mechanical or chemical irritation of the basal portions of the brain. Injection of water also produces a rise of temperature, the cause of the so-called water-fever probably being the presence of minute traces of organic matter in the water used for injection. Excessive loss of water may lead to elevation of body temperature. According to Barbour the causation of fever is as follows:—Due to the infection, some metabolic changes occur in the tissues which increase their affinity,

especially that of muscles, to water. The blood volume, therefore, becomes decreased and there is a redistribution of circulation chiefly at the cost of the peripheral circulation. The skin becomes cold and the heat regulating mechanism interprets it as it interprets ordinary cold and raises the body temperature. The important change that occurs in fever is, therefore, change in blood volume. This may follow loss through diuresis, or excessive sweating or restriction of fluid intake.

Fever may be continuous, remittent and intermittent. The temperature may fall by lysis or crisis. The febrile temperature is primarily due not to an increase in the heat production or to an absolute inefficiency in heat dissipation but to a lack of adjustment between the two. The heat regulation in fever behaves as if the regulatory centres were set to maintain the body temperature at a new level, which is maintained in the same way as normal temperature. Some of the recent writers, however, speak of an increased excitability of the heat centres which causes them to regulate the body temperature at a new and higher level. In fever the heat regulation is less perfectly adjusted than in health as it is much more difficult to reduce the temperature of a healthy man than a fevered individual either with cold baths or with antipyretic drugs. The extra heat produced within the body is also less perfectly eliminated.

Metabolism is accelerated in fever as warmed tissues metabolise more material than cooled tissues, but in addition to this there is probably a toxic element that causes tissue destruction, and the rapidity of protein consumption varies in different infections. This increased metabolism rarely exceeds 40 or 50 per cent. over normal. No strict parallelism exists between the rate of protein decomposition and elevation of the temperature. The amount of protein lost to the body may be considerable, being as much as 200 to 500 gm. of muscle-tissue per day. In surra more than one-fifth of the proteins of the body are lost in the course of the disease. Immediately following the cessation of fever there is a marked increase in the nitrogen excretion. The nitrogenous equilibrium can be maintained in fevers and the patient's strength conserved by giving adequate diet, but unfortunately in many fevers the toxins produce loss of appetite which prevents intake of food and a decrease in absorption may occur. The partial starvation thus produced increases protein metabolism; besides high temperature produces further rapid wasting of tissues. To supply this need administration of glucose and other similar foods is necessary. It has been demonstrated that by giving selected carbohydrate food not only is nitrogenous equilibrium maintained, but the abnormal excretion of creatinin, which is probably derived from the breakdown of muscle-tissue, is reduced. This does not bear out the toxic or essential protein destruction in fever.

Acidosis also occurs in fever but its occurrence is probably not as common as is supposed. Ketonuria which often occurs in febrile conditions is an indication of disturbance in fat metabolism, but is not considered as evidence of acidosis. It is not possible to make any generalisation regarding the occurrence of acidosis or alkalosis in fevers.

It is well known that excretion of chlorides in fever is decreased. This is certainly true of pneumonia and other infectious diseases. The retention of salt is associated with simultaneous retention of water, especially in long continued fever such as typhoid; the tissues, therefore, become relatively rich in fluids and poor in solids. A normal individual will excrete up to three litres of water which may be introduced into his body; the fever patients do not do this and retain a considerable amount. The extra water is, however, stored mainly in the tissues and less in the blood and the same is the case with the chlorides. The state of affairs is, therefore, different from what occurs in nephritis where the concentration of the salt is high in the blood. It has been shown that antipyretic drugs bring about a dilution of the blood, which favours dissipation of heat by radiation.

Effects of fever. Heat above normal body temperature, especially if continued for a long time, causes degenerative changes in the tissues. The cells undergo cloudy swelling. The proteins of the muscles coagulate at 104°F . (40°C .) and in nearly all tissues globulin coagulates at 45°C .; mammalian muscle passes into rigor between 45° to 50°C . Coagulation takes place at a lower temperature when continued for a long time. Even if coagulation is not visible a change analogous to it may cause death of the cells. It is possible that heat and toxin may act in a synergistic manner to disturb the functions of the cells.

The heat also acts directly on the heart muscle and stimulation of the nerve centres controlling the heart produces slowing or acceleration. When temperature is the only factor, a rise of temperature, *e.g.*, 97.8° to 104°F . (37° to 40°C .) will cause an increase of pulse rate. In addition to this, toxins play a part, *e.g.*, in typhoid fever the pulse is relatively slow, being about 70 to 80 beats per minute with a temperature of 103° to 104°F . In scarlet fever the pulse is surprisingly rapid.

As regards the central nervous system, the toxins and other pyretics are said to produce a stimulation of the regulatory mechanism. A number of drugs, *e.g.*, cocaine, atropine,

caffeine, epinephrine, which are known to stimulate the central nervous system, cause a rise of temperature, while those which depress the nervous system, *e.g.*, alcohol, chloral, morphine, cause a fall of temperature. The mechanism of production of fever seems to be a stimulation of the sympathetic system to which the heat regulating mechanism probably belongs. The other convulsant poisons such as santonin, picrotoxin and phenol, which stimulate the para-sympathetic system, and cause myosis, slow pulse and psychic depression, do not increase the temperature.

The significance of fever. The practical question involved in the treatment of infectious diseases is to what extent should one attempt to reduce the temperature. It was thought that the febrile rise of temperature was on the whole a favourable manifestation and helped the organism in overcoming infection. Clinical experience shows that when bacterial infections are unaccompanied by fever they run a very unfavourable course. Leprosy, tuberculosis and parasitic diseases not marked by febrile reactions are usually difficult to cure and do not confer immunity. Treatment of neurosyphilis by artificial infection with malaria probably chiefly acts by increase of temperature. Collapse may occur in certain conditions if the stimulus of high temperature is removed. It has been shown that with most bacteria the optimum temperature for development is confined within very narrow limits, which are exceeded by the temperature of fever. The tendency of fever may, therefore, be useful, but unfortunately the cells of the organism are not adjusted to work under high temperature and it may be more detrimental to them than to the bacteria. It has been advocated by some that fever is the essential manifestation of infection, that it is dangerous in itself, and should be vigorously combated. The question still remains unsettled, as patients with a high temperature are more sick than those with a low temperature, but this is not due to the temperature but because such patients are suffering from more severe infections. Besides this, in the most unfavourable of all infections the temperature may be low. From a comparison of clinical cases it is, therefore, not possible

to judge the favourable and unfavourable effects of temperature. The antipyretic measures also do not give any clear answer, because not only do they reduce the temperature, but they have various effects on other parts of the body, especially the brain and the circulation.

Many experimental studies have been carried out in this connection. Rabbits have been kept with a body temperature of 41°C . (105.8°F .) and over for weeks at a time without any serious damage. The degeneration of internal organs observed in infectious fever is not due to prolonged overheating of the body. Serious effects are only produced when the temperature is raised to a height not usually encountered in fevers. The damage appears to be done more by the infection. The question is, does the rise of temperature exert a favourable or an unfavourable effect upon the course of infection? The high temperature may have a direct effect on the infective organism or it may help the host in developing protective mechanisms. The temperatures encountered in certain fevers are sufficiently high to inhibit the growth of certain bacteria. Pneumococcus and gonococcus do not grow well at a temperature of 104°F . (40°C .) or over. The course of infections in animals artificially infected with pneumococci and diphtheria is said to be favourably affected by artificially raising their body temperature. It has also been shown that with moderate overheating 103.2° to 104°F . (39.5° to 40°C .), the formation of agglutinins, bacteriolysins and anti-toxins is increased. From the results of these experiments it is concluded that moderately high temperature, even though maintained for a long time, is not in itself a dangerous manifestation. In artificial infections in animals an increased temperature has a favourable effect on the course of the infection and increases the speed with which the protective anti-bodies are formed. In the treatment of fevers, therefore, one should not try to bring down a high temperature too vigorously unless it is above 105.8°F (41°C .). In such cases the reduction of temperature is comparative; but in ordinary febrile temperatures there is no need for active interference. The value of antipyretic measures in such cases is to be judged, not solely from their

effect in reducing the temperature, but also from their effect on the general condition of the patients and especially on their nervous system and circulation.

Antipyretic measures. The temperature of the body can be lowered by factors which decrease the production of heat or increase its loss. As the temperature tends to fall below normal, compensatory reactions are at once set up to keep the temperature normal. It is not found possible to depress the temperature without effecting profound changes. On the other hand, it is relatively easy to lower an abnormally high temperature because it coincides with the natural tendency to return to the normal or physiological state. Antipyretics, therefore, have no effect on normal temperature but readily act when pyrexia is present. Antipyretic measures can be divided in three main groups:—

(1) Those that abstract heat, *e.g.*, application of cold in form of baths, sponging, packs. This subject has been discussed in the chapter on physiotherapy.

(2) Those that increase the dissipation of heat by dilating the cutaneous vessels and by restoring the water content of the blood. Their action is mainly central. These are antipyretics of the coal tar group, *e.g.*, acetanilide, phenazone (antipyrin), phenacetin.

(3) The cinchona alkaloids, especially quinine, probably diminish heat production. Salicylates, aconite and veratrum probably diminish heat production by slowing the circulation.

THE ANTIPYRETIC DRUGS

High temperature in the old days was chiefly combated by baths and giving such vegetable alkaloids as aconite and quinine. Bass (1875) discovered that salicylic acid and related bodies produce a fall of temperature in fever. Most of the modern antipyretics were discovered in an attempt to synthesise quinine. A large number of bodies were introduced, but those of importance are acetanilide, phenazone, phenacetin and amidopyrin or pyramidon. These are all benzol derivatives and prepared from aniline. Phenol, guaiacol, salicylates and many other compounds also lower febrile temperature, but they are

much inferior. All these drugs have the same action. The antipyretic drugs are divided into three groups:—

(1) The essentially antipyretic drugs are, (a) acetanilide and acetophenetidin or phenacetin and (b) antipyrin and amidopyrin also known as pyramidon; they are also analgesic. Like alkaloids these are precipitated by tannic acid, alkalies and other alkaloidal precipitants.

(2) The anti-rheumatic group consists of salicylic acid and its derivatives such as acetylsalicylic acid (aspirin), etc. Cinchophen or atophan also comes under this group.

(3) The antimalarial antipyretics, *i.e.*, the cinchona alkaloids.

Acetanilide. It is a colourless crystalline substance. The dose is 2 to 4 gr. (0.12 to 0.25 gm.). It has a slight biting taste and is soluble in 1 in 190 of water. It is rapidly absorbed from the gastro-intestinal tract and more rapidly if given subcutaneously. The antipyretic action is thought to be due to para-amino-phenol, and varies directly with the rapidity with which this substance is formed in the body. Temperature reduction may be so rapid as to produce collapse. For this reason its use has been to a great extent discarded.

Acetophenetidin or phenacetin. Phenacetin is a white crystalline powder. The dose is 5 to 10 grains (0.3 to 0.6 gm.). It is much less toxic than acetanilide. It produces a feeling of drowsiness and, therefore, acts as a mild hypnotic; it has a much more powerful action on neuralgic pains than any of the other antipyretics. It is an ideal antipyretic in that it produces a gradual but persistent fall of temperature and does not produce collapse. It does not produce cyanosis and has less tendency to cause skin eruptions and profuse sweating.

Antipyrin or phenazone. It is derived from phenyl hydrazone; the dose is 5 to 7 grains or more (0.3 to 0.5 gm.) and its action is very similar to acetanilide.

Amidopyrin or pyramidon is a derivative of antipyrine. It is given in doses of 5 grains (0.3 gm.).

These drugs have no effect on the normal temperature. Antipyrine is more analgesic in neuralgic pains and neuritis originating from the spinal cord than acetanilide, and is, therefore, largely used in the shooting pains of tabes which it may not always relieve. Phenacetin is used more for headaches. Phenazone is slightly less toxic than acetanilide and little more than phenacetin. A large number of combinations of antipyrine have been put on the market, *e.g.*, salipyrin is a combination with salicylic acid. Antipyrine affects the circulation and the kidneys slightly and can be prescribed in heart disease and nephritis. It is not very irritating to the stomach. It has been used in tuberculosis, typhoid

fever, erysipelas and pneumonia but it should be given with great caution.

Cryogenin occurs in crystalline masses and is slightly soluble in water. It has been used as an antipyretic to control high temperature, and this is found valuable in the treatment of phthisis and lingering pyrexia that sometimes follows the acute stages of an infection. The dose is 3 to 24 grains, but it should not generally exceed 10 to 15 grains daily.

Salicylates. These compounds lower the febrile temperature promptly. The mode of reduction is very much like that of the members of the coal tar group, *i.e.*, increased loss of heat by dilatation of cutaneous vessels and increased perspiration. In healthy individuals this is compensated for by increased heat production so that the normal temperature remains unaffected. Salicylates may easily take the place of other antipyretics and are probably safer; but may produce unpleasant side effects. Small doses of acetylsalicylic acid or aspirin (5 to 10 grains) are commonly used in mild fevers and not only reduce temperature but also unpleasant symptoms such as headache. Novaspirin (methylenecitralsalicylic) has no advantage.

Cinchophen and neocinchophen. Cinchophen or atophan is phenylcinchoninic acid. It has a biting bitterish taste and is irritating to the stomach. It has a pronounced action on the liver cells and increases the quantity of bile. Its absorption from the intestine is irregular and uncertain, and some can be recovered from the urine. Cinchophen is an antipyretic, but its chief action is an analgesic in rheumatism and as a mobilizer of uric acid. The dose is 5 to 15 grains (0.3 to 1.0 gm.).

Neo-cinchophen is an ethyl ester. It is also called novatophan and tolysin. It is tasteless and does not irritate the stomach. It has also a cholagogue action and has less destructive effect on the liver cells than cinchophen. The dose is 8 to 15 grains.

Both these compounds are chiefly used in rheumatism and gout.

Quinine. The antipyretic action of quinine has been dealt with in another section. In malaria, quinine reduces the temperature because of its effect on the malarial parasites, but in addition it has a general antipyretic effect in fevers other than malaria. Large doses of quinine are said to depress the metabolism by 10 per cent.; the heat loss appears to be but little altered. Quinine has also a sedative action on the centres though it is not so marked as with other antipyretics. Quinine, however, conserves energy probably by decreasing metabolism instead of increasing the heat loss. In such diseases as influenza when the depressant action of the aniline drug is undesirable, quinine is very useful. The antipyretic dose is 5 to 15 grains.

Antipyretic action of analgesic antipyretics. In normal persons even large doses of these drugs produce no effect. In fever a fall is produced beginning within 2 hours and lasting for 2 to 4 hours.

The fall is accompanied by profuse perspiration due to dilatation of cutaneous vessels and increased heat loss owing to direct action of the drug on the heat regulating centres. Barbour studied the effect of direct application of these drugs to the region of the heat centres and found that both the antipyretics and narcotics produced a fall. Central nerve stimulants such as caffeine produced a rise. The mechanism of rise of temperature is a stimulation of these centres and the antipyretics, therefore, act by depressing them.

Untoward and toxic effects. Some individuals show an idiosyncrasy to these drugs, cyanosis and collapse being produced with ordinary therapeutic doses. Papular and erythematous skin rashes may follow phenazone and acetanilide, antipyrin produces a scarlatiniform rash with oedema of the face and fever. It may also produce urticaria, or a vesicular, bullous or eczematous eruption. A large number of headache powders contain acetanilide and deaths have occurred from their use, the chief symptoms being cyanosis, nausea, persistent vomiting, weak and irregular pulse, dyspnoea, cold sweat, coma and collapse. Deaths have occurred with 5 grains (0.3 gm.) but recovery is reported after 120 grains (7.5 gm.). Severe symptoms often follow from 0.2 to 1.0 gm. doses. Antipyrin may cause burning and swelling of the whole alimentary tract, with nausea, vomiting, diarrhoea, skin rashes, mental dullness, tremors, cerebral convulsions, coma and death from failure of respiration. In the case of amidopyrin, excitement, increased reflexes, and a measles-like eruption have been noticed.

Acetanilide and phenacetin produce acute and chronic poisoning; in one form collapse and cardiac failure being prominent features and in the other cyanosis accompanied by anaemia, emaciation and weakness. There is dyspnoea and the heart is rapid and weak. The cyanosis is said to be due to the formation of methaemoglobin, but it is probably produced by para-amidophenol or some other aniline derivative which has been found in the blood and urine; sulphhaemoglobinemia is said to be present. Methaemoglobin has, however, been seen spectroscopically. Cyanosis may persist for weeks after the drugs are stopped. Caffeine is often combined with these drugs to prevent depression, but it is said to increase the toxicity of acetanilide. Sodium bicarbonate is believed to lower their toxicity.

Treatment consists in washing out the stomach with alkaline solution, maintenance of body temperature and combating the collapse with atropine, caffeine, strychnine, digitalis, etc. Chronic poisoning is met with, the symptoms being cyanosis, anaemia, disturbance of digestion, headache, dyspnoea on exertion, weak pulse, extreme muscular weakness.

Habit formation. Habit with these drugs is formed by nervous patients suffering from headache, neuralgia, etc. The habits show mental depression, digestive disturbances, anaemia and general weak-

ness. The habit is not vicious like the morphine habit but it may be difficult to break.

Therapeutic Application of Antipyretic Measures

Treatment of fever. From the foregoing discussion it is obvious that pyrexia alone does not constitute the sole indication for treatment. The toxic state of the patient is a more important factor. When it is desired to reduce temperature it is advisable to control it by use of cold sponging or bathing. Antipyretic drugs should be resorted to as little as possible. The objection to these is that they depress the patient and decrease his power of resisting disease.

In all fevers, especially when they are prolonged, water should be freely given whether the patient asks for it or not. Not less than two quarts should be given to an adult daily. It is not only essential to flush the kidneys and remove toxins circulating in the blood, but it is essential for the proper functioning of the body. The turnover of the fluid during digestion has been estimated at five quarts per day, of which no less than one quart is bile, the fluid being excreted and reabsorbed. Considerable quantities of water are lost in the urine and respiration and a certain amount in normal stools. In heat elimination an important factor is the distribution of water in the body. By dehydrating a dog a high temperature may be produced. The fever is caused by blood concentration and checked by blood dilution. In fever produced by intravenous injection of coli vaccine and in other fevers, the temperature is reduced by measures which produce dilution of the blood. In influenza, typhoid, pneumonia, salt fever, inanition fever and other fevers, the blood has been found to be concentrated, the reason being a special affinity of the tissue colloids for water. When the volume of the blood is diminished, the viscosity is increased and the surface flow of the blood decreases. The result is diminished sweating and consequent diminished heat elimination and fever. The dilution of the blood by increased ingestion of fluids remedies these defects, increases heat elimination and lowers temperature. According to Barbour, fever therapy consists in supplying water to the tissues and the

intravenous administration of water in high fever may save life. He considers that antipyretic drugs, such as acetanilide, acetophenetidin, antipyrin, sodium salicylate, aspirin and cinchophen act in fever by lessening the blood concentration and thus increasing heat elimination. After a dose of aspirin, the heat production is decreased by 4 per cent., but heat elimination is increased by 38 per cent. In non-febrile patients, in whom there is no dehydration, there is no fall of temperature in equivalent doses. Fever patients are found to be still sensitive to these drugs during temporary cessation of the fever and during convalescence.

Analgesics in the treatment of fever. The chief use of antipyretic measures is reduction of temperature in febrile conditions, but antipyretic drugs have also a sedative action on the nervous system. When the temperature is high enough to produce nervousness, headache and discomfort, antipyretics by reducing the temperature, quieting the nervous system and relieving pain, promote well-being and aid in recovery. Rapid reduction of temperature is, of course, essential in case of sunstroke, for if this is not done the temperature rises steadily till the patient dies. Such cases can only be treated by cold sponging or cold baths. There is general agreement that antipyretic drugs are of little value in the treatment of severe fever, when the temperature is retained at a high level for many weeks. Such cases are benefited by cold sponging or cold baths. Even if the bath may not produce a prolonged lowering of the temperature, the short fall gives the organs of the body rest and the results are very satisfactory. The chief use of antipyretic drugs is in mild cases of fever and in these they generally make the patients more comfortable and often assist in producing sleep, though they may not influence the course of the disease. They neither strike at the cause of the fever nor at any symptoms other than those resulting from hyperpyrexia. They make the type of disease neither less severe nor shorter. For instance, in malaria, antipyretics may prevent the development of the paroxysm but they do not attack the cause of the disease. They are merely a symptomatic and not a specific mode of treatment and symptomatic treatment should

always be carried out with care, as more harm than good may be done. When it is not possible to attack the cause of the disease it is advisable to remove the objectionable symptoms. This they do by their sedative action on the pathologically stimulated centres and on the sensory part of the cerebral cortex. Schimidberg gave them the name of "fever narcotics" and this is a very suitable name, as now-a-days they are seldom employed to combat hyperpyrexia, but rather in hope that the patient will be benefited by their sedative action on the symptoms of fever due to hyper-excitability of the brain centres. They decrease pain in the limbs, headache, delirium, and restlessness, clear confusion of mind, and induce sleep. The effects of these drugs vary with the individuals, some people can take large quantities without effect, while others are affected by small quantities. According to Barbour the analgesic effects of these drugs are produced by decreasing the concentration of the blood. Others consider that they relieve intracranial pressure.

When antipyretic drugs are used, it is better to give a small dose before resorting to a large dose. Special care is taken when these are given in diseases where the temperature falls by crisis as a dose before the crisis may produce dangerous collapse by exaggerating the physiological fall.

In cases of pain and discomfort without fever, such as headache, migraine, neuralgia, muscular rheumatism, pains of locomotor ataxia, dysmenorrhœa, and in various nervous conditions, in chorea, whooping cough, diabetes insipidus, antipyretic drugs especially acetyl salicylic acid (aspirin) generally give relief. Pyramidon is said to be a specific for measles. The drugs are usually given in the form of capsules or tablets for internal use and are sometimes combined with codeine, bromides, etc., if necessary. On account of their depressent action on the heart these drugs are often combined with cardiac tonics such as caffeine and digitalis.

HEAT STROKE (SUNSTROKE)

If heat loss is prevented, the body temperature rises, e.g., if a normal man is immersed in a hot bath up to the neck the body temperature rapidly rises from 37°C. to 38°C. (98.4°F. to

100.4°F.) or to 40°C. (104°F.) or even higher, according to the temperature of the bath. This is what sometimes happens in those living in hot climates and heat stroke is the result. The most common form of heat stroke is what is commonly known as 'a touch of the Sun.' The milder cases are termed heat exhaustion. It follows generally after an individual has been exposed to the Sun and glare. There are two forms: (1) Mild form. The patient suddenly becomes acutely sensitive to heat and feels weak; there may be nausea, headache, dizziness, pain in the limbs, thirst and sleeplessness. He may either collapse in the Sun or may drag himself into the shade before collapsing. The pulse is at first rapid and weak, the skin is clammy, the respirations are shallow and hurried, the pupils are dilated and the temperature is normal or subnormal. The mortality in this type is very low, but the patients often recover slowly. (2) Severe form. This is frequently fatal. The symptoms start as in the mild form but consciousness is lost early, the skin becomes dry and hot, and the temperature rises very rapidly. The pupils are dilated, the pulse becomes rapid and full, and the breathing is deep at first but later shallow and finally of the Cheyne-Stokes type; the pupils become contracted and the conjunctiva injected. The urine and stools may be passed involuntarily, there may be muscular twitchings and rocking of the head. Epileptiform convulsions may occur and death follow.

The temperature usually is between 99.1° to 104.7°F. (37.3° to 40.4°C.). In severe forms the body temperature rises rapidly from 104° to 111.2°F. (40° to 44°C.), rarely to 114.8°F. (46°C.). If the temperature does not rise beyond 111.2°F. (44°C.) recovery is possible under vigorous hydrotherapeutic treatment. When the temperature exceeds this limit recovery is rare, the patient as a rule becoming comatose, pale, livid and cyanotic. A dry, cool or pale skin indicates that the maximum heat dissipation is not taking place and shows that the normal mechanism of heat regulation has become deranged. Among the most common causes of sunstroke are continued high temperature with high humidity (exercise in warm weather with

unsuitable clothing). Heat prostration is not uncommon among soldiers after long marches in full uniform. It also occurs in those individuals whose regulating mechanism against excessive heat is less perfect. Alcohol is an important predisposing factor because it lessens the effectiveness of the regulating mechanism by depressing the heat regulating centres and paralysing the cutaneous vessels. When the patient's temperature is brought down by vigorous hydrotherapeutic measures he may show continuous fever for days or even weeks after the acute hyperpyrexia has subsided. During this time the body temperature is extremely sensitive to external influences, and for years afterwards these patients may show increased sensitiveness to heat. All these factors show that heat-stroke is usually associated with and is followed by a marked disturbance in the heat regulation of the body, the centres which regulate the heat loss being deranged.

Treatment. In mild cases if the patient is put in a cool place and is given drinks of cold water, he often improves. If the pulse remains weak give a diffusible stimulant such as half a drachm each of aromatic spirits of ammonia and spirits of ether, or an injection of camphor in oil. Sometimes in these cases the temperature falls to much below normal and it is necessary to apply heat to the body, and hot drinks have to be given. The patient should be carefully watched as a sudden rise of temperature may occur.

When hyperpyrexia is present such stimulants as caffeine, or camphor in oil should be given at once. Every effort should be made to bring down the temperature as soon as possible. For this purpose the patient is put in a bath of water at 50°F. (10°C.) and he is kept there till the rectal temperature falls to 102°F. (38.8°C.). When this temperature is reached the body will probably continue to lose heat in favourable cases after removal from the bath, even sometimes to below normal. While the patient is in the bath his body should be vigorously rubbed because unless hyperemia of the skin is produced by this procedure the overheated blood will be driven to the internal organs by the contraction of the blood vessels. Rubbing the body with

ice or placing the patient in a sheet wrung out of iced water are less efficient than the bath.

An enema of 2 or 3 pints of ice cold water is often very useful. When ice is not available the heat should be abstracted from the body by evaporation of water. This is done by spraying water from a fine nozzle on to the stripped surface of the body, a current of air being maintained by hand or electric fans. Equally good results are obtained by wrapping the patient in a sheet wrung out in water and putting him under a fan. Tepid water by this method will remove as much heat as ice cold water. This method is very effective and is now extensively used in hospitals. When the rectal temperature has reached 102°F. (38.8°C.) the evaporation is stopped. Cessation of sweating is a sign of impending recurrence. Such patients should at once be covered with a moist sheet and put under a fan. Once the artificial perspiration is established recurrence is often averted.

STOKER'S CRAMPS

This is the type of heat exhaustion seen frequently in labourers working in engine rooms or in deep mines where the temperature is high. The patient gets muscular twitchings for a time and is then siezed with violent cramps principally of the abdominal muscles. The spasm may involve other muscles and may become so general as to resemble an epileptic attack. Other symptoms are nausea, dizziness and stupor, the patient being usually pale and perspiring. The pulse is rapid but strong and the temperature only slightly above normal. The condition is believed to be due to loss of chlorides to below normal by excessive ingestion and excretion of water.

Treatment. The patient should be removed to a cool place and should be given plenty to drink. Slow injection of 3 or 4 pints of slightly hypertonic saline is useful. Salt added to the drinking water (0.25 per cent. or 10 gm. per gallon) is useful in preventing attacks and is recommended as a prophylactic measure for stokers, coalminers, etc. Each person is provided with two quarts of water to which two teaspoonfuls of common salt have been added.

In addition to the various causes of hyperpyrexia already mentioned, there may be certain other types of fevers, the etiology of which is imperfectly understood. Low persistent fever or an evening rise of temperature may occur in tropical climates, in persons who are run down or have recently suffered from a prolonged attack of fever. This is probably due to the heat centres not acting effectively and can be controlled by sending the patients to a cool climate such as a hill station.

CHAPTER IX

PAIN AND INSOMNIA

Insomnia and the Use of Hypnotics

Sleep is one of the primary necessities of human life. Loss of sleep or prolonged deprivation, leads to many pathological changes in the body. Normal sleep is a protective mechanism by which the physiological wear and tear of the body are made good. It appears at definite times and if unsatisfied, will pass off; but frequent abstinence leads to permanent derangement of body function. Prolonged sleeplessness causes various pathological changes, such as histological changes in the cerebral cortex and probably the appearance of a toxin in the blood.

Sleep is a condition of unconsciousness to surroundings. There are many theories as to the etiology of sleep. Muscular relaxations, rise in the intra-cranial pressure, cerebral anæmia and similar other theories have been advanced. Cerebral anæmia will undoubtedly produce unconsciousness and sleep, but the natural sleep is not, however, attended with any material alteration in the cerebral circulation. Knowledge regarding the mechanism of sleep is still very scanty. The nervous system acts as a whole. Pathological and experimental lesions in the infundibular region produce pathological sleep. A diencephalic sleep centre has been described but the term waking centre would be more appropriate. Presence of sleep suggests an abeyance of the katabolic activity associated with the sympathetic system and an excess of the anabolic activity associated with the parasympathetic system. The diencephalic centre is stimulated by sensory impulses from many directions. Insomnia might be due to excessive cortical activity, and for this there is no need to use drugs strong enough to depress the diencephalon.

Others regard sleep as a rhythmic depression of the activity of the brain and insomnia as due to one or a combination of two causes: abnormal afferent stimuli affecting the brain at a time when its depression is due or increased excitability of the brain cells. The rational treatment of the first type is to remove the stimuli if possible. Increased excitability may be congenital or acquired; there are brains which are easily kept awake from childhood. Excitability can be in-

creased artificially, as by caffeine, ephedrine, and high blood pressure. Bromides are especially valuable for normal brains kept awake by such stimuli as worry.

The treatment of insomnia is of importance. Many of the chronic invalidating diseases, such as chronic malaria, kala-azar, ankylostomiasis are accompanied by loss of sleep and the practitioners are confronted with the problem of procuring rest for the body, in addition to finding some specific remedy for the malady. The use of hypnotics is not, however, always indicated and treatment may be described under two heads.

1. **General measures.** For minor ailments, such as flatulence and distension of the stomach no hypnotic drugs are called for, careful regulation of the dietary together with some gastric sedative will relieve the condition and help to produce sleep. In cases where the specific cause of sleeplessness is untraceable, a careful survey has to be made as regards any unusual mental stress or strain which may be responsible for the loss of sleep.

General hygienic measures, regular and careful dieting, exercise in the open air without involving any physical fatigue, will be effective in those cases where insomnia is due to overwork and prolonged mental exertion. A holiday in the country, in the hills, or at the seaside are often the most successful remedy, although some hypnotic may be necessary some time or other to supplement the effect. Besides conditions that favour relaxation, viz., a quiet room, and a suitable bed will be of great help.

2. **Drugs.** Insomnia being a very common complaint, there is a great demand for some safe and reliable hypnotics. There are quite a large number of compounds on the market and they are mostly similar as regards their general property. According to Clark the properties of an ideal hypnotic are:—(1) The drug must produce a reliable hypnotic effect. (2) The hypnotic action must be produced without a preliminary stage of excitement. (3) The drug must not irritate the stomach. (4) The drug must be absorbed readily, so that the hypnotic action is produced at a regular interval after the administration of the drug. (5) The drug must either be broken down in the body or else be excreted rapidly, so that it produces no after effects next day, and does not produce cumulative poisoning when taken daily. (6) The drug must not produce

dangerous side actions, such as cardiac depression. (7) There must be a sufficient margin of safety between the dose required to produce hypnosis and that which produces medullary depression. (8) The drug must not produce tolerance, nor a drug habit, when given regularly over long periods.

There is no drug, which possesses all these qualities together and it is only after prolonged use that some of the disadvantages are found out.

The important thing is to know the cause of insomnia; the cause should be treated, and hypnotics should only be used when general measures fail or are inapplicable. Drugs of low toxicity include the inorganic bromides (*e.g.*, sodium, potassium, ammonium, strontium, and calcium bromides), alcohol, phenazone and its derivatives, aspirin and salicylic acid derivatives. Combinations of these with opium preparations or codeine are often effectual. The great change during recent years has been the production of large numbers of barbituric acid derivatives and the introduction of basal anaesthetics, many of which are being used as hypnotics. Other hypnotic drugs of varying degree of toxicity are the alcohol-chloral group—chloral, chloralamide, chloralose, butyl-chloral, chloretone, hypnal, dormiol, isopral, ural, bromal, amylene hydrate, paraldehyde, aponal, neuronal, hedonal, avertin. The urea group includes urethane, aponal, aleudrin, adalin, bromural, somnosal; and the sulphone group sulphonal, trional, tetronal. Chloral and chloralamide are good hypnotics which have dropped out of use. Avertin (tri-brom-ethyl-alcohol) is as toxic as chloroform. Care and experience are required to decide on suitable doses. The members of the urea group are safe and are not very toxic. The sulphone group is not much used; these drugs are slowly absorbed and there is a danger of cumulative effect.

The barbituric acid group offers a most formidable list of preparations. When a higher allyl group than ethyl is introduced the drug becomes much more toxic. The compounds of these drugs with analgesics are dangerous because of the risk of overdose of hypnotic while a large enough dose of the analgesic is being given. Barbiturics are rapid and certain in their action. They act much more quickly on an empty stomach or if taken with alcohol. Idiosyncrasy to these drugs occurs and might be natural or acquired; any indication of allergy, hyperthyroidism, or latent liver or renal dysfunction is a danger signal. Full doses of a basal anaesthetic are very dangerous in the presence of any of these danger signals, but a smaller dose will produce an adequate effect. Any prolonged toxic condition renders these drugs much more active. They may produce nerve paralysis and after large doses coma may set in. There is not much risk of cumulation, and very little tolerance is as a rule acquired. Habit formation undoubtedly occurs; if they are taken regularly every night it is common for an

overdose to be taken sooner or later. Many cyclical cases get an obsession of insomnia and no drug would put them to sleep.

Analgesics might produce sleep by reducing afferent stimuli and can be usefully combined with hypnotics, but a fixed inflexible combination is dangerous. A small analgesic dose of morphine combined with chloral might be more effective than a large dose of the either drug alone. Combinations of hypnotics acting at different points are also useful. Salicylates have a special property of diminishing painful stimuli and thus act secondarily as hypnotics.

Chloral hydrate. The hypnotic effect is produced with doses of 10-20 grains by the mouth in ten to fifteen minutes' time and sound sleep in an hour. It lasts several hours resembling the normal physiological sleep and the patient can be easily and completely aroused and awaken refreshed without any depressant after-effects. It may also be given per rectum and this method is the only channel of administration in eclampsia, and in convulsions of tetanus where the oral method is impossible and the hypodermic route too irritant to be of practical use. The dangers of depression of the heart and respiration with chloral are over-rated and it can be considered a safe hypnotic if it does not overstep the therapeutic limit.

Butyl chloral hydrate. The hypnotic effect of this drug is of shorter duration and the depressing effect on the heart is more marked. It is said to be particularly useful in facial neuralgia in doses of 5 to 20 grains.

Chloretone. The action is similar to that of chloral hydrate, but it is probably more toxic; it is largely used as a gastric sedative and also to prevent sea-sickness, in doses of 5 to 20 grains.

Chloralamide. This compound is a combination of chloral hydrate with formamide. It is prescribed in doses of 15 to 30 grains but is probably less effective as a hypnotic than chloral hydrate.

Other related compounds such as chloralose, isopral have been prepared. But they appear to have no advantage over chloral hydrate.

Paraldehyde. It produces natural sleep in 15 to 20 minutes lasting for several hours, but the effect of the drug is less certain than chloral hydrate and it has no analgesic action. It is said

to produce no depressing effects on the heart and respiration in therapeutic doses and can, therefore, be safely administered in cases complicated with heart disease. The disadvantages of the drug is that it has got a very unpleasant taste which, however, can be rectified by giving it in some flavouring agent. Prolonged use of paraldehyde leads to irritation of the throat and stomach, an unpleasant odour in the breath, dizziness and faintness, and a habit not unfrequently develops.

The dose of paraldehyde for single administration is one drachm (4 c.cm.) and in some cases two drachms may be given. In cases where the drug has to be given repeatedly, one teaspoonful every hour should be given till sleep is produced.

Sulphone group. Sulphonal is insoluble in water and is absorbed very slowly from the gastro-intestinal tract. Hence there may be delay in producing the desired hypnosis after a dose of sulphonal which must, therefore, be properly timed. The sleep that is produced, lasts for six to eight hours and sometimes the effect may be continued for the next 24 hours. On account of its slow rate of excretion, the drug tends to produce cumulative effects and may give rise to signs of poisoning.

Sulphonal is prescribed in nervous disorders when chloral hydrate is contra-indicated. It is also useful in cases of insanity to control the excitable symptoms. The ordinary dose is 10 to 15 grains (0.75 to 1.0 gm.) and in urgent cases as much as 30 grains (2.0 gm.) may be given preferably in warm milk before bed-time. This drug should never be continued for more than a week at a time as cumulative effect may set in. Trional and Tetronal have been used but have little advantage over sulphonal.

Urea derivatives. Urethane and the other related urea derivatives have very feeble hypnotic action. They are not now used in therapeutics.

Barbituric acid derivatives. Barbital is diethyl barbituric acid or diethyl malonyl urea. It was introduced by Emil Fischer and Von Mering in 1903 under the name of Veronal. Barbital is the chief hypnotic of malonyl urea series, though its introduction was immediately followed by other barbiturates.

Action and uses of barbiturates. The hypnotic and sedative action of the barbiturates is responsible for their extensive use in various ailments to produce calmness and sleep, to suppress convulsions and even to produce partial or complete anaesthesia. With ordinary doses their analgesic effects are not marked but they can be advantageously employed with other analgesic drugs so as to potentiate the action of the latter. If taken on an empty stomach or with alcohol their effect is accelerated. The effect of a dose is prompt, securing dreamless sleep in about half an hour after oral administration, and immediately after intravenous use. The sleep lasts for four to eight hours, varying with the individuals and with the preparation used. The patient generally awakens refreshed, but in some cases there may be a feeling of lassitude, vertigo and headache. Generally there are no undesirable side effects with most of these drugs; only in some cases the duration of narcosis may be prolonged. There is not much risk of accumulation with these drugs, it was not so much the drug itself that accumulated as the effect. There is very little tolerance of these drugs but habit-formation undoubtedly occurs.

The barbiturates, such as barbital and phenobarbital are generally given at bed-time to insure natural sleep. With the other barbiturates the duration of sleep and the after inertia is shorter. These drugs may be administered by all channels, such as by the mouth or the rectum, hypodermically or by the intravenous route. As hypnotics they are probably more effective and somewhat more analgesic than chloral hydrate and the margin between the ordinary therapeutic and toxic dose is considered to be wide enough. The chief conditions for which they are employed are to dull worry and excitement, to calm nervousness and obtain tranquillity and rest. They may, therefore, be used in hyperthyroidism, chorea, hysteria, neurasthenia, in epilepsy in the intervals between the seizures, in mental disturbances and in impending delirium tremens.

Cautions and contraindications: Cases of poisoning from the use of barbituric-acid derivatives including barbitone (veronal), medinal, luminal, nembutal, amytal, etc., have been

observed very often and great care should be exercised when prescribing these drugs. The average fatal dose for barbitone is about 50 gr., although death has occurred after such small a dose as 15 grains. There is always danger of cumulative effects and of habit formation when these drugs are taken in therapeutic doses on successive nights. Moreover, in addition to their specific hypnotic action, these drugs also have effects on the lungs, heart and kidneys. Larger doses and in susceptible individuals smaller doses, may cause inflammation of the lungs, while heart failure and even death may sometimes supervene from toxic effect on the myocardium. The kidneys may be injured and suppression of urine may result; this has been observed especially after administration of nembutal.

Certain conditions which greatly modify the action of these drugs should also be borne in mind. Thus the effects of barbituric-acid derivatives are greatly enhanced in hyperthyroidism or when toxæmia is present; an ordinary normal dose may then produce dangerous symptoms. Patients with exophthalmic goitre are very susceptible to nembutal and administration of even 6 gr. doses has been followed by fatal results. These drugs should always be avoided in cases of renal and hepatic insufficiency.

Barbital. The hypnotic action begins in about half an hour apparently with little after-effects and it is considered quite safe. Long-continued use should be deprecated, and in patients with cardio-renal disease it must be given with caution as excretion is delayed.

As a hypnotic veronal is best prescribed in the form of a powder, to be given in hot fluid, such as hot milk, half an hour before bed-time in doses of 5 to 10 grains (0.3 to 0.6 gm.). Ordinarily 5 grains are sufficient to produce sleep and more than 20 grains should not be given in 24 hours. Pills or tablets should be crushed before swallowing to insure absorption.

Veronal sodium. Synonym—*Medinal*. This drug, it is claimed, acts more rapidly on account of its greater solubility. Even small doses, such as 1 grain three times daily, in some cases produce a lengthy sleep. It is stated that toxic symptoms

do not appear with less than 15 grains daily, whilst an adequate sedative effect is obtained with small doses.

Nembutal. Synonym—*Pentobarbital sodium* ; *Sodium iso-amylal*. Its action and uses are essentially similar to those of barbital, but it is effective even in smaller dosage. The action is of relatively brief duration, which is an additional advantage, especially when relatively large doses have to be administered. It is now used exclusively as a sedative, particularly before local, general or spinal anæsthesia and as a hypnotic in various mental disorders. The dose is $1\frac{1}{2}$ grains in capsule by the mouth. In maniacal cases about 3 grains can be given which can be cautiously increased by $1\frac{1}{2}$ grains till the desired effect is produced.

Amytal. The general action and uses of amytal are similar to those of barbital. It is used as a sedative and hypnotic in insomnia and as a preliminary medication to surgical anæsthesia. The sedative dose is $\frac{1}{3}$ to $\frac{3}{4}$ grain (0.02 to 0.04 gm.) twice or thrice daily by the mouth with water or hot milk; as a hypnotic $1\frac{1}{2}$ to 5 grains (0.1 to 0.3 gm.) should be given before bed-time.

The mono-sodium salt of iso-amyl-ethyl-barbituric acid is on the market under the name of *sodium amytal*, and is a sedative hypnotic.

Luminal. Synonym—*Phenobarbital*. Luminal is used as a useful hypnotic in conditions of excitement, in sleeplessness associated with pain, migraine, chorea, neurasthenia, in convulsions of children, in mental conditions and various other disorders. Its chief use is as a sedative and antispasmodic in the treatment of epilepsy, in which it lessens the frequency and severity of seizures. In simple insomnia, $1\frac{1}{2}$ to 5 grains (0.1 to 0.3 gm.) dissolved in hot water are given, and where there is excitement as much as 10 grains may be administered but should be used very cautiously.

Luminal-sodium or phenobarbital sodium is a soluble preparation of luminal and has been used intramuscularly in epilepsy. It has the same action and uses as luminal but it is said to be more efficacious in epilepsy. The drug is best given

in solution with hot milk or water in doses of 1 to 2 grains once a day usually at bed-time.

The disadvantage of luminal and its sodium salt is that they are liable to produce scarlatiniform rashes resembling measles. It has been observed that the effective dose of luminal is very near the toxic dose and continuance of the drug for more than a week may produce toxic symptoms.

Bromides. These are not, strictly speaking, hypnotic drugs, but they depress the motor functions, leading to a condition of dullness and apathy which conduces to sleep and is, therefore, particularly useful in nervous insomnia. The effects are generally different from those of the other hypnotics, the bromides produce a mental calm, progressing to sluggishness, lack of attentive power and muscular weakness. All these dispose towards sleep. If the dose is not excessive, perception, observation, and motor functions are not interfered with, but with excessive doses or after prolonged administration, psychic depression and confusion of speech are evident. As hypnotics bromides of sodium, potassium and ammonia are generally used. They are quite effective in doses of 15 to 30 grains, given one to two hours before retiring. In epilepsy, the bromides prove very successful in quite a large percentage of cases. In most cases the attacks become milder and less frequent, and may be suppressed for the time being. Bromides have, however, little action on pain.

Hyoscine. In cases where insomnia is due to acute mania it is used as a powerful narcotic. It is said to increase the action of the heart and circulation without producing any effect on respiration or causing dryness of the throat. In the dose of as little as $1/480$ grain it produces its brief mydriatic effect within 18 minutes. It should be avoided in glaucoma.

In all cases where there is a condition of cerebral hyper-excitability, *e.g.*, in chorea, diathermasia (thermal stroke) acute mania, delirium, tremors and post encephalitic Parkinsonism, hyoscine is indicated in doses of $1/50$ to $1/200$ grain hypodermically.

Pain and the Use of Analgesics

The commonest and the most important symptom for which medical aid is sought is pain. Pain causes intense suffering and a good deal of exhaustion and is a condition which demands instant relief. It is the sacred duty of the medical profession to try to relieve pain by all the remedial means at their disposal. Attempts have been made for a very long time to find drugs which will relieve pain and lessen the suffering of the patient. Opium, the pain-relieving drug *par excellence*, was discovered years ago but time has shown that there are many limitations to its safe administration. The advance of modern organic chemistry has brought within our reach a host of new synthetic analgesic remedies, which though not as potent as opium derivatives are very useful in a variety of conditions. A short review of these developments should, therefore, be found useful to the practitioners.

The opium alkaloids. Opium contains a large number of alkaloids which belong to two groups. The phenanthrene pyridine group includes morphine, codeine, thebaine, etc., and the benzyl-isoquinoline group comprises narcotine, papaverine, narceine, etc. Morphine is the most important of the opium alkaloids as a hypnotic and analgesic; but it is the most depressant while codeine has a much feebler depressant action, and thebaine is a definite convulsant.

Morphine and opium are used to lessen pain and to procure sleep in all conditions due to pain and disturbing influences. They relieve pain more efficiently than any other drug and is in fact the only remedy available when others fail. The opium alkaloids have been indiscriminately and injudiciously employed in therapeutics. It should be remembered that the relief of symptoms from morphine is only temporary, and persistent use of the drug may do definite harm by obscuring the diagnosis. The danger of habit formation should also be borne in mind and it is in cases of neurotic individuals and in chronic diseases that the habitual use of the drug leads to addiction.

For the relief of pain opium and morphine surpass all other analgesics. For oral use, Tincture of opium (5 to 15 minims) or

Liquid hydrochloride of morphine (10 to 60 minims) can be used. Hydrochloride or sulphate of morphine in doses of $1/8$ to $1/4$ grain hypodermically generally suffices to dull the sensation of pain and produce sleep. Omuopon and alopon are preparations containing all the alkaloids of opium, which can be given either by the mouth or subcutaneously in doses of $1/6$ to $1/3$ grain, and are said to disturb digestion less than morphine alone. In cases of insomnia the use of these drugs should only be advocated when it is due to pain, cough, dyspnoea and other urgent symptoms, the cause of which cannot be controlled immediately. In nervous insomnia and in psychic excitement morphine should not be given. Smaller doses should always be tried and morphine is best combined with atropine ($1/100$ grain) to counteract the depressing effect on the respiratory centre.

Morphine derivatives. A few compounds have been synthesized from morphine with a view to finding a remedy which will produce the therapeutic effects of morphine without having any tendency to respiratory depression or to production of drug-habit. Though a large number of such derivatives have been prepared, in fact no derivative has been found which combines in itself all the advantages of morphine and yet does not share the disadvantages of the latter. Codeine or its salt codeine phosphate, in doses of $1/4$ to 1 grain, is less narcotic, less constipating and is believed to be less liable to produce a habit. Its use is, therefore, steadily increasing. Heroin is diacetyl morphine and resembles morphine in its general action but is more depressant to the respiratory centre. The dose is $1/25$ to $1/8$ grain, and for hypodermic use $1/12$ grain should be given. It shares in fact all the disadvantages of morphine without having any advantages over it. Heroin, however, is such a dangerous drug of addiction that its use should be permitted only under strict medical supervision. Dionin is ethyl morphine and stands intermediate between morphine and codeine. A few oxidation products of morphine have been recently prepared; they are dilaudidide (dihydromorphinone) and dicodide (dihydrocodeinone). They are all habit-forming and have no special advantage. The

following table from Clark (1933) gives the expert report of the League of Nations (1931) about certain morphine derivatives.

Drug	Mean therapeutic dose in grammes	Relative toxicity	Relative power of producing addiction	Relative action as analgesic	Relative depression of respiration and cough	Relative depression of gut movement
Morphine	0.02 gm.	1	1	1	1	1
Codeine	0.04 „	$\frac{1}{2}$	very slight	very slight	$\frac{1}{2}$ to $\frac{1}{4}$	$\frac{1}{2}$
Heroin	0.005 „	5-10	2-4	2	2	very slight
Dicodide	1.005 „	...	$\frac{1}{2}$?	1	?
Dilaudide	9.008 „		$\frac{1}{2}$	1	$\frac{1}{4}$	very slight

Aromatic analgesics. A large number of coal tar derivatives are commonly used to lower temperature and to relieve headache and pain. They have analgesic effect against neuralgic and muscular pains, headache, migraine, cold, etc., but are often ineffective if the pain is due to some injury.

Aspirin (acetyl salicylic acid), is the most popular remedy for headache in doses of 5 to 15 grains. Nothing very definite is known as regards the etiology of headache. A rise in the pressure of the cerebro-spinal fluid is a frequent cause of headache while the spasmodic contraction of the cerebral vessel may probably be responsible for migraine. The manner in which these drugs act is uncertain, and Barbour believes that acetyl-salicylic acid causes a transference of water from tissue into blood and thereby relieves headache. The depressant effect of the drug on the heart precludes its continuous use. Phenazone or antipyrin and phenacetin were formerly used as analgesic to relieve headache, migraine, facial neuralgia, etc., but they are now less frequently used. Pyramidon or amidopyrin acts similarly to phenazone and is effective in doses of 5 to 8 grains. It is an efficient analgesic and its toxicity is very low. Veramon is a combination of amidopyrin with diethyl barbiturate and is said in many cases to relieve pain as well as morphine; Allonal, a combination of allyl isopropyl barbituric acid with amidopyrin has both analgesic and hypnotic effect. Cibalgin, a compound of amidopyrin with dial, is given in doses of 4 to

16 grains. Compral, a new analgesic, is a combination of pyramidon with trichlorethyl urethane for use in pain generally; one to two tablets of $7\frac{1}{2}$ grains each will be useful.

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CHAPTER X

TONICS

The word 'tonic' is commonly used by physicians and by the laity at large to denote remedies which stimulate the protoplasmic activity of the tissues, thereby increasing the general metabolic processes of the body. Tonics are generally employed in conditions of asthenia, neurasthenia and general depression of the body activities after illness, strain and effects of climatic conditions. In tropical climates one frequently meets with cases who are victims of chronic maladies or have become debilitated by living in a hot and damp atmosphere. Good nutritious food and rest, combined with tonic drugs, go a long way towards curing this condition. Tonics produce a sense of well-being, increased strength and vitality by stimulating the functional activity of the digestive organs as well as by improving the general condition of the hæmopoietic system. They contribute towards the improvement of the general tone of the run-down body or some of its component parts. Tonics are, therefore, classed as general tonics, digestive tonics, cardiac tonics, hæmatinics, nervine or nerve tonics and so on. It should be realised, however, that the convalescent from disease improve more by adequate rest, proper selection of nutritious and easily digestible diet and good hygienic surroundings than by tonic drugs alone, which only aid and speed up the process.

GENERAL TONICS

The drugs classed as tonics are very large in number, but here we will only discuss a few of the important ones, whose action can be explained rationally.

Bitters. These are always prescribed to patients convalescing after long protracted illness, where there is a definite derangement of the digestive functions and an upset of the general metabolic processes of the body. They are used to improve the appetite of such patients and are generally given before a meal. They produce a reflex flow of the gastric juice which is bene-

ficial to the impoverished digestive process. The effect of these drugs is never due to direct contact of the drug with the oxyntic cells of the glands in the gastric mucosa, but is entirely reflex through the gustatory nerves. The common bitter substances in use are gentian, quassia and calumba, while many of the bitter alkaloids, such as the cinchona alkaloids and strychnine, are commonly employed for their bitter action in small doses.

The preparations of cinchona and quinine are employed in very small doses to stimulate the gastric mucosa; they thereby increase secretion, improve appetite and aid digestive processes. The infusion of cinchona is an excellent stomachic in cases of mild gastric catarrh and atonic dyspepsia. The compound tincture in combination with *nux vomica* is often used as a general tonic and appetiser. In all post-febrile states, in convalescence from prolonged illness, in general debility and cachexias from various chronic maladies, quinine is often prescribed as a tonic in conjunction with *nux vomica*, iron and arsenic. Though quinine is believed to be a cardiac depressant, the drug in small doses acts as a sedative and by slowing down the pulse improves the irregularity in rhythm and is thus beneficial to the heart.

Strychnine. Preparations of *nux vomica* are often prescribed for their simple bitter action. They always invoke a reflex flow of the gastric juice and tone up the muscular wall of the viscus, thereby improving the appetite and aiding the digestive functions of the patient generally. Strychnine is thus used in atonic dyspepsia and during convalescence from acute illness. Besides its bitter properties, strychnine is often used as a tonic to the nerves and the muscular system. It diminishes the 'synaptic resistance' in the nervous system, whereby a smaller stimulus can pass a greater number of synapses than before and bring into action more nerve fibres. It has, therefore, been used in post-diphtheritic paralysis of muscles and post-operative paralysis of the stomach and gut. It is a good tonic for sexual debility, impotence and spermatorrhoea. Strychnine is often reputed as a cardiac tonic, but views are very conflicting regarding its direct effect on the heart. Experiments show that the drug has no direct effect on an isolated

perfused heart; in fact, it depresses it. It is, however, held that the drug does indirectly improve the heart beat through its stimulating effect on the medullary centres. The drug is undoubtedly an emergent cardiac tonic, as when injected with atropine in threatening cardiac failure, it will almost immediately raise the tone of the organ and strengthen the pulse. Injections of strychnine are useful in weakness of the heart in acute fevers, such as pneumonia, influenza and diphtheria. It is held that the drug increases the blood pressure by its effect on the medullary centres and in this way improves the nutrition of the myocardium by improving the coronary circulation. Strychnine is also a useful respiratory stimulant in chronic bronchitis, pneumonia and emphysema. As a general tonic and stimulant of metabolism, strychnine is invaluable. As a tonic in cachexia and general debility, it should be given in very small doses. In convalescence from exhausting illness associated with anæmia, strychnine is invaluable as a general tonic and hæmatinic in combination with iron and arsenic. Strychnine is a tonic in the real sense of the word, in that it increases the tone of all stripped and unstripped muscle tissue in the body which is lowered after disease and other debilitating conditions.

Alcohol. It has long enjoyed the reputation of being a good tonic. It is often used in cases of chronic debility and various wasting diseases. It has been shown that regular use of moderate doses of alcohol with meals promotes digestion, increases appetite, checks waste, favours deposition of fat and so alcohol practically possesses all the properties of a true food. It is a food in the sense that it is readily oxidised, yielding considerable energy, which is only available for immediate emergency use and cannot be stored as a reserve for future use.

Alcohol excites a psychic secretion of gastric juice and it can also produce a direct stimulant action on the fundus of the stomach, causing an abundant secretion of dilute gastric juice. Apart from being a digestive stimulant, it is also used as a restorative tonic in urgent cases of fainting or threatening cardiac failure due to shock, hæmorrhage, etc. Here it acts as a diffusible stimulant reflexly and thereby increases the pulse rate, blood pressure and respiration.

Alcohol is contained in various tonic wines sold in the market and is often prescribed for convalescing patients. It should always be given in small and frequently repeated doses even in health, as given in this way, it is completely metabolised. If larger quantities of alcohol are taken, its toxic effect over-balance any of the beneficial effects produced.

Thyroid. The use of endocrines as tonics is of very recent origin. They appear to form a system which regulates the rate of metabolism, and the growth and development of the body. Thyroid is reputed to be the most powerful tonic of all the endocrine glands. It has been considered as the trigger gland of the body, which sets other endocrines to action. Besides its use in thyroid deficiency diseases, it is often prescribed as a tonic to neurasthenic patients, suffering from general prostration and in whom energy and appetite are lacking. It is invaluable to convalescing patients and to fatigued subjects after long-continued strain and over-work. In tropics, due to the enervating influence of the climate, such cases are frequently met with and the drug in small doses has given most encouraging results. It acts by increasing the rate at which energy is produced by the body. Administration of thyroid adds more fuel to the fire of metabolism in the body and the oxygen intake rises. The body-machine is geared at a higher level, and food normally used to supply the current demand for energy and stored as fat, is now used to yield more energy and only a small proportion is reserved for future use. Appetite is thus increased, patients feel more energetic and the gland now serves the purpose of a tonic in the right sense of the word. The drug should be prescribed in doses of $\frac{1}{2}$ to 1 grain twice daily for this purpose for a period not exceeding a fortnight at a time.

Arsenic. The drug is a true digestive tonic and when given in small doses ($\frac{1}{50}$ gr.) it acts as a stomachic by its local action on the gastric mucosa. When given before meals it stimulates appetite and aids digestion by increasing the activity of salivary, peptic and intestinal glands. Medicinal doses improve local circulation and nutrition of the tissues and increase deposit of adipose tissue. As a general tonic in com-

bination with strychnine, it is of value in depressive psychoses of old age, and those that follow acute infections, such as influenza and typhoid fevers, in neurasthenia, hypochondria and melancholia and in cachexias of maladies like chronic malaria, syphilis, etc.

Calcium. Calcium compounds have a great reputation as tonics. Calcium is a normal constituent of the body tissues and is indispensable to the life of all organisms. The calcium content of the body is about 2 per cent. of its entire weight. The nerve and muscle cells require an optimum concentration of calcium for their proper functioning, and so calcium is the best tonic for the neuromuscular mechanism of the body. The compounds of calcium promote nutrition, improve cardiac and vascular tone. In pulmonary tuberculosis, where the excretion of calcium is excessive, a prompt and adequate supply of the drug is essential and favours the process of healing of tubercular lesions. Calcium lactophosphate and glycerophosphate with cod-liver oil and ultra-violet therapy are very useful in rickets and malnutrition. Marked improvement is noticed in secondary anæmias with combined therapy of calcium, iron and arsenic. Calcium should always be given along with parathyroid for its efficient assimilation in the body and can be prescribed with advantage in all conditions of debility where the body metabolism is distinctly sluggish.

Iron. Iron is a general tonic and a hæmatinic. It is a natural constituent of the body and is a food; the amount of iron necessary to keep a person in normal health is 1/11 to 1/8 gr. daily. The tone of the nervous system is improved with iron therapy in cases of mental overwork, neurasthenia and neuralgia, because it stimulates the body metabolism. In combination with arsenic, strychnine and quinine, it is prescribed with benefit in all forms of debility with or without anæmia, and where there is a general lack of tone in the tissues. In all conditions where there is loss of appetite and sluggishness of body functions, iron therapy is beneficial. The importance of iron as a hæmatinic has been dealt with under anæmia.

Phosphorus. Phosphorus is the normal constituent of most tissues and it exerts a stimulating influence, when administered in small doses, upon their nutrition. This is most marked as regards the nervous and the osseous system. Phosphorus has been regarded as a useful tonic and restorative in neurasthenia or nervous debility, when the system is weakened by anxiety, overwork or sexual excesses. In anæmia, in combination with iron, small doses are said to be beneficial. Phosphorus is recommended as a restorative after typhoid fever, as it is believed to hasten the convalescence. In cases of chronic malaria, phosphorated oil is considered to be of value. During medication by phosphorus, the patient should be watched for the first symptom of overdose. The drug should never be given in large doses and is not indicated where acute or inflammatory lesions are present. It should be given in form of alcoholic or oily solution.

Phosphoric and hypophosphorus acids and their preparations are also useful as general tonic. It is stated that the morbid conditions in which these are most beneficial, are those in which there is demineralisation of the organism with hypo-acidity of the urine. The lactophosphates and hypophosphites are simply convenient modes of administering calcium, potassium and other substances, while phosphorus acts as a stimulant to bone growth and not by its deposition in the bone. This difference between these salts and phosphorus should be clearly borne in mind.

CARDIAC TONICS

Physiological considerations. The circulatory system with the lungs may be regarded as a single functional system, which supplies oxygen to the tissues and removes carbon dioxide from them. They are efficiently controlled according to the needs of the body from time to time by a central and a local mechanism. The heart forms the central and the most important organ in the system and continues functioning regularly and efficiently throughout life without ever resting. Normally, in a healthy adult, it makes on an average about 103,680 contractions a day, though these considerably vary in different stages of life and in diseases. The capacity of muscular exertion of an

individual in health and the fate of the patient in disease, all depend on the condition of the heart. The heart is characterised by its unique properties—namely, automaticity or stimulus production, rhythmicity, excitability, contractility, tonicity and conductivity.

Various theories have been advanced to explain the origin of heart beat. It is regarded that the initial stimulus leading to heart's contraction is inherent in the specialised contractile cardiac tissue as is evidenced by the fact that heart starts beating in the foetus, *in utero* even before the development of the nervous system. Embryologists hold that it is the primitive embryonic tissue in the pace maker of the heart that is responsible for the origination of the initial beat of the heart. The heart beat originating in the sino-auricular node, situated at the junction of the great veins at the base of the heart, passes as a wave of contraction over the musculature of the auricles. It then reaches the auriculoventricular node, where a little delay occurs, but thence the wave rapidly passes along the specialised conductive tissue, namely, the bundle of His and the Purkinje system. The wave of excitation is accompanied by a change in electric potential, which can be demonstrated by the string galvanometer. The interval between the commencement of the auricular and ventricular contraction is about 0.15 second. The contraction of the heart is then followed by an absolute refractory period, during which the cardiac muscle is incapable of further excitation. The heart recovers its power of excitability earlier than the contractility and the duration of the refractory period depends on the period of rest. The force of contraction of cardiac muscle and its oxygen consumption depend on the initial length of the muscle fibres. The efficient and a powerful contraction of the left ventricle of the heart depends on an adequate inflow of the venous blood into the right auricle. Any increase in the amount of venous inflow will distend the chamber of the heart more and consequently will increase the oxygen consumption required to supply the energy for doing the extra work as a pump to maintain an efficient circulation for the body tissues. The heart has the first call of blood leaving it by the aorta and as much as 20 per cent. of the total output may enter the coronary circulation. Unlike voluntary muscles, heart can never enter into oxygen debt. Hence a deficiency in oxygen supply to its need will result in an accumulation of lactic acid definitely depressing and injuring the efficacy of this vital organ. A deficient coronary circulation will impoverish heart from lack of proper nutrition and the whole body will share the misery.

The heart has great reserve power to meet the demands of emergencies and utilises only a fraction of it for its work, when the body is at complete rest. It has been found that the oxygen consumption during complete bodily rest is $\frac{1}{4}$ litre per minute, a heavy meal

increases to $\frac{1}{2}$ litre a minute and walking at the rate of three miles an hour increases it to 1 litre. An athlete with a large heart has immense reserve powers, his pulse rate is slow at rest, but the stroke volume of the heart is great, and hence the circulation volume is sufficient to meet the requirements of the body tissues. The reverse is the case with a non-athlete with a small heart. His reserve power is small and is rapidly and easily exhausted after moderate exercise as manifested by the signs and symptoms of loss of compensation. Even in some pathological hearts, the compensation is not lost, and the heart can still supply the oxygen needs of the body at rest. Clark states that in failure of the vasomotor mechanism, some injury to the cardiac valves, poisoning of the cardiac musculature and disordered cardiac rhythm are the possible factors responsible for failure of circulation. In shock and other allied conditions, the capillaries lose tone due to paralysis by some toxin or local metabolites resulting in stasis of the blood in the capillary bed. The venous inflow and the filling of the heart become deficient, the organ beats strongly to compensate the situation but with no effect, the coronary circulation suffers, the heart lacks nutrition and ultimately a vicious circle is established, in which the whole system partakes.

The action of the heart is also regulated by two sets of nerves, namely, the sympathetic and the vagus. The sympathetic is the augmentor nerve of the heart, it increases the force of contraction of both the auricles and the ventricles, and the rate of conduction from auricle to ventricle. The vagus is the inhibitor nerve of the heart, it slows the heart, depresses the force of beat of the auricles and also the rate of conduction from the auricle to the ventricle. The vagus has a constant control over the activity of the heart; the control is slight at two extremes of life and maximum in early adult life. The vagus also constricts the coronary arteries and the sympathetic dilates them. In spite of the regular and constant nervous control over the heart's activities, the pace maker of heart has a natural rhythm, irrespective of any nervous control.

The demand of the tissues for oxygen varies from minute to minute, and this is regulated by the blood flowing through the small arteries and the arterioles. The distribution of the blood is so efficiently made that the organs, whose continuous activity is most essential to the maintenance of life, receive the major share most promptly and regularly. The central nervous system deserves a foremost mention. Arrest of circulation in the brain only for a few seconds will result in unconsciousness. The brain regulates the general supply of the blood to other organs after ensuring a rich supply for itself. The body mechanism is so adjusted that the demand for blood supply is met in emergent cases for some particular functioning organ at the expense of the other. This is met with by a proper regulation of the arterioles

mostly by a central and a peripheral mechanism. The arterioles are very richly supplied with vasoconstrictor nerves and by their action as well as by the vagal and vasomotor centres in the medulla, the general blood pressure and the supply of blood to different organs of the body are determined. The arterioles supplying the most vital organs of the body, the constant activity of which is most essential to life, are not supplied by the vasoconstrictor nerves. The velocity and pressure in the blood vessels decrease as they branch and become smaller, but remain considerable as far as the arterioles. The arterioles terminate in thin-walled capillaries, which perform rhythmic contractions. At rest, only a small number of them dilate to carry on the circulation to distant parts, while when an organ functionates, the arterioles supplying it dilate and a greater number of capillaries open, and the blood flow to the organ increases manifold. The normal circulation of the blood depends on the maintenance of a certain amount of tone in the capillaries and the veins, failing which the blood stagnates and the heart does not receive adequate quantity of blood to contract upon and to carry on its proper function.

The splanchnic vessels are richly furnished with vasoconstrictor nerves, and next come those supplying the skin and the muscles. It is stated that the blood flow through the skin and muscles at rest is 12-10 c.cm. per 100 grm. per minute, liver and kidney 70 c.cm., brain 150 c.cm. and the endocrines 600 c.cm.

Heart-failure

The failure of the heart to maintain an efficient circulation in the body is not an uncommon complication in diseases. A knowledge of the remedial measures for the maintenance of the heart's action will, therefore, be very useful to the physician practising in the tropics.

From the clinical point of view the following types of cardiac failures are met with :

(1) Acute cardiac failure causing sudden death ; it occurs in angina pectoris, ventricular fibrillation and coronary disease. Acute failure is also produced by chloroform, lightning or electrical shock.

(2) Sub-acute cardiac failure occurs in acute infectious diseases, e.g., pneumonia, typhoid, diphtheria, influenza, etc.

(3) Chronic cardiac failure usually occurs in chronic valvular disease and myocardial lesions.

In considering the treatment of heart-failure it should be remembered that the essential cause of heart-failure lies in the heart muscle. The physician should, therefore, focus his attention on it with a view to avoiding further embarrassment of the heart, and in order to promote the efficiency of the myocardium.

The treatment of heart-failure may be conveniently described under the following heads:

General management. When the heart is compensated, careful instructions should be given to the patient regarding his mode of life. It is of vital importance that he should have abundance of physical and mental rest in his daily life. Excitement, anxiety, worry and emotional strain should, as far as possible, be avoided. He should not have any physical exertion that would give rise to breathlessness, palpitation, fatigue, a sense of tightness across the chest, or precordial pain. At the same time a certain amount of graduated exercise is desirable. Walking on the plains is preferable to hill-climbing. When the cardiac affection is progressive, the amount of exertion must be correspondingly reduced. With regard to diet, the food should be nutritious, easily assimilable and not likely to cause indigestion. The fluid intake should be restricted. A carbohydrate diet is bulky and apt to cause flatulence, while a high protein diet increases the resistance in the peripheral circulation. The diet should, therefore, be a mixed one with predominance of the albuminous element. A careful search should be made for a septic focus, which should, if possible, be eradicated. The bowels should be kept open and regular.

Drugs. The underlying idea of treatment with drugs should be, (a) to give rest to the heart as much as possible, (b) to improve the nutrition of the heart and thereby enable it to do more useful work, (c) to increase the force of systole and prolong diastole, thus improving the efficiency of the contractions and lengthening the period of rest. There is a great deal of confusion as to what drugs should be classed as true tonics to the heart. The word 'cardiac tonic' usually conveys the suggestion that an increased activity or tone is being brought on slowly, but which is more enduring, while 'cardiac

stimulant' means a prompt but transient increase in the activity of the heart which is not enduring. Gunn (1928) suggests three possible definitions for those drugs which are used to combat failing circulation. "Firstly, a drug may directly or indirectly increase the output of the heart and under this most of the cardiac tonics are included. Secondly, drugs may increase the 'minute output' by some action on the heart or its nerve supply, and under this may be included such drugs as adrenalin, ephedrine, atropine, ammonia, etc. Lastly, there is a class of drugs which will be regarded as true stimulants, if they produce an increased ventricular pressure by a primary effect on the heart operating under the constant dynamic condition." It should be borne in mind that the idea of treatment of heart-disease is not to increase the frequency of a failing heart, because thereby the process of exhaustion is hastened.

During the compensated stage, no cardiac tonics are required. Tonics, such as iron, arsenic and phosphorus, may be taken from time to time; while in children, cod-liver oil, the syrup of iodide of iron are of special advantage.

Digitalis. The most useful drug for failing compensation is digitalis. In the words of Mackenzie, "Digitalis, acting on the vagus, pulls the reins of the heart, acting on the heart muscle it is a most useful whip, at the same time providing it with food by improving the circulation. By slowing the heart it makes it regular and also this gives the heart an opportunity of resting, so secondarily improving the contractility, conductivity and excitability of the organ."

Lewis writes, "The giving of digitalis to unselected heart cases is much to be deplored. Those who regard digitalis as a cardiac stimulant, mistake its character; its chief action is to rest the heart. To the heart, foxglove is not tonic, but powerfully hypnotic. It controls the diastole of the heart: it extends the period of ventricular sleep."

There are two conditions in which digitalis is indicated: (1) Heart-failure, specially of the congestive type, with cardiac dilatation, diminished contractility and tonicity of the heart muscle, anuria and anasarca. Mitral cases, with water-logging, and cases of auricular fibrillation, with a ventricular

rate exceeding 80 per minute, react better than aortic cases. (2) Presence of a chronic auricular fibrillation with tachycardia, where heart-failure has not supervened. Such cases may be kept going and heart-failure postponed indefinitely by adequate digitalis medication directed to maintain the ventricular rate below 80 per minute at rest. Provided congestive heart-failure is present, hypertension and aortic regurgitation are not contraindications, as was formerly taught. The results, however, in the above two conditions, as well as in agina pectoris, are not always as favourable as in the mitral group.

Patients put on digitalis for the first time, should go to bed and remain there until the reaction to the drug has been investigated fully. As a routine, the tincture of digitalis, biologically standardized, should be used. A usual and safe dosage for an adult is 60 minims of the tincture daily, by mouth. This may be given divided into two or three doses, diluted with water, and not mixed with other medicines. A daily dose of one fluid drachm meets the requirements of most cases and, for the busy practitioner is simple to calculate and remember.

According to Eggleston the average amount of the drug required to digitalise the human heart is $9/40$ grain of the powdered digitalis or $2\frac{1}{4}$ minims of the tincture per pound body weight. In estimating the weight, the amount of fat and œdema must not be taken into account. In non-urgent cases, one-fourth of the calculated dose is given at once, one-fourth after six hours, and thereafter one-tenth to one-eighth of the total every six hours. But in urgent cases, one-third to one-half is given at once, six hours later one-fifth to one-fourth and after another six hours one-eighth to one-sixth.

The Eggleston method of heavy dosage and rapid digitalization is reserved for the cases 'in extremis' and should be adopted only where the patient can be examined at least twice every day. Ordinarily, the daily dose of 60 minims of the standardized tincture should be continued until either the desired slowing of the heart rate is obtained, or, until nausea or diarrhœa appears.

In Europe and U.S.A., on the average, a total dose of about 7 fluid drachms in 7 days is required to get the reaction. In India, however, the required dose is very much higher due to rapid deterioration and loss of potency of the drug in the tropics. Bose (1925) concluded: (i) The total quantity of the active standardised tincture of digitalis required exceeds 14 drachms given in 14 days: that is, more than twice the dose must be given in India to obtain results. (ii) To obtain prompt results, this tincture should be used in doses of 2 or 3 drachms per day for 5 days. (iii) Heart-failure with normal rhythm requires the same high dosage as with auricular fibrillation, and the response to digitalis is good. (iv) The stage of optimum benefit with digitalis nearly merges into the stage of minor intoxication. (v) With a good tincture, a dose of 30 minims a day can be given indefinitely without toxic effects, because the same amount is daily used up in the body. (vi) Apart from the typical slowing of the heart rate and coupled beats, digitalis may, at times, provoke a sudden regular paroxysmal tachycardia of 180 beats per minute, which is dangerous to a failing heart. (vii) In Europe, more than 50 per cent. of all cases of heart-failure have auricular fibrillation; in India, however, the incidence of auricular fibrillation is about 10 per cent. only, or less.

In recent years *Digitalis lanata* has come into use. It is a potent source of glucosides, stated to be nearly 4 times as potent as *D. purpurea*. *D. lanata* contains four glucosides, of which the chief is *lanadigin*. It is only one-third as toxic as strophanthin; it accumulates in the body more than strophanthin, but much less than the *purpurea* glucosides. Clinically, it is said to act more rapidly than any of the *purpurea* preparations, and the nature of action is similar.

Recently, Bose has worked out the total dose required to produce the digitalis reaction, with the various tinctures, on the basis of one fluid drachm a day. *Digitifortis* (P. D. & Co.) is the most potent of all, being 150 per cent. the standard laid down in the British Pharmacopœia, and one obtains a reaction with six drachms in six days. *Digitutin* (B. W. & Co.) and *Pandigal* (Biersdorf) require a dose of 9 drachms in 9 days, and are weaker preparations, but they are well tolerated in toxic gastritis. For intravenous medication, *Digoxin* (B. W. & Co.) is the most powerful, but *pandigal* and *nativelles digitalin ampoules* are also useful; they are less

dangerous than strophanthin intravenously and in febrile and toxic hearts, are equally beneficial.

Strophanthin. Strophanthin has the same action as digitalis, the standard tincture (dose 2 to 5 min.) acts in $\frac{1}{4}$ to 1 hour, but the effects are unreliable and it is often ill-tolerated. Strophanthin 1/250 grain intravenously is generally given in heart-failure to obtain immediate results. Caution has, however, to be exercised, as the drug sometimes behaves in an unaccountable manner, loss of consciousness has followed an ordinary dose in a weakened patient. It should always be well diluted with 10 c.cm. of normal saline, and injected, very slowly, into the vein. In acute febrile heart-failure, sudden death has rarely occurred with intravenous strophanthin.

Camphor and its derivatives. Camphor is now-a-days largely used in the treatment of heart-failure, especially in chronic myocarditis with simple cardiac insufficiency. In typhoid and pneumonia it is considered as a valuable stimulant to the heart. With regard to its effect on the heart, no decisive and accepted proof has been obtained of any direct action on the organ. Given subcutaneously, camphor acts as a local irritant and reflexly stimulates the medullary centres. The evidence available suggests that it does not directly stimulate the heart, but like alcohol causes redistribution of the blood, which will benefit the patient generally and the heart-beat particularly. It is now generally employed in doses of one to one and a half grains, dissolved in 1 c.cm. of ether or olive oil, and injected hypodermically.

Among other camphor preparations 'coramine' has been given in shock and cardiac weakness resulting from infectious diseases. It has a stimulating action on the central nervous system and on the circulatory and respiratory apparatus. By the mouth 1 to 2 c.cm. of the liquid may be administered and 1 c.cm. of the ampoules may be given hypodermically, intramuscularly or intravenously, according to the gravity of the situation. Cardiazol (Metrazol, pentamethylene tetrazol) is another general circulatory tonic acting similarly. Tablets, 0.1 gm., may be given by mouth or 1 c.cm. of solution in ampoules may be given subcutaneously, 3 to 4 times daily.

Caffeine. Caffeine is a direct cardiac stimulant acting on the excito-motor area of the heart. It produces an increase of the pulse rate, but from the point of view of rational treatment, stimulation of the heart alone will be of little value unless the circulation is improved as well; its efficacy is, therefore, doubted. Caffeine sodium salicylate or caffeine sodium benzoate in doses of 2 grains may be injected subcutaneously to produce stimulation of the heart. But this action is of relatively little value, because in a failing heart, the increase in frequency, leads to exhaustion.

Adrenalin. It is a peripheral sympathetic stimulant. It augments and accelerates the cardiac beats and is one of the most potent therapeutic agents to resuscitate a failing heart. The action and uses of adrenalin are so well known that it is unnecessary to consider them in detail, but there are a few points about its clinical use that are not well appreciated. Adrenalin, when given hypodermically or intravenously, especially by the latter route, causes vaso-constriction and raises the blood pressure, and consequently in damaged myocardium it may throw a sudden heavy strain on the heart and thereby do positive harm. The action of adrenalin is transient and, except in conditions where there is low blood pressure with feeble heart-beat, no permanent improvement in circulation is brought about. It has, however, been used repeatedly and often with success, in threatened or complete arrest of the heart, when that is not due to fibrillation. Intravenously, adrenalin acts almost immediately. The dose should be about one-fiftieth of that of the hypodermic dose, and there is no remedy available that bears comparison with it in such cases. Intracardiac adrenalin to resuscitate the patient in cases of arrested heart-beat or in anæsthetic syncope, has been useful in many instances. The dose of adrenaline by the subcutaneous route is $\frac{1}{4}$ c.cm. or less. Dr. Hurst, of Guy's Hospital, states that 3 to 5 minims is the optimum and effective dose even in severe spasms of asthma. Hurst finds that dose higher than $\frac{1}{4}$ c.cm. causes shock, rigor, and profound bodily tremors and depression for many hours after. For intravenous purposes, a dose

of 2 minims diluted with 2 c.cm. of distilled water, is given very slowly.

Adrenalin is very unstable in neutral or alkaline solutions and in such solutions it is very readily oxidised to form inert substances. The solution turns brownish with age and the deterioration in potency is proportional to the discoloration and any solution thus discoloured is unsuitable for use.

Ephedrine. The vaso-pressor effect of this drug is now well recognised. It is used by some clinicians to guard against heart-failure in pneumonia and influenza; $\frac{1}{4}$ to $\frac{1}{2}$ grain three times daily is effective in cases of low blood pressure. The advantages of ephedrine over adrenalin are that it can be given by the mouth and produces an action of much longer duration. The toxic effects of the drug should, however, be borne in mind.

The author has shown that pseudo-ephedrine has a direct stimulant action on the myocardium. A tincture made from ephedra, which contains both ephedrine and pseudo-ephedrine, has been used with success in epidemic dropsy, pneumonia, diphtheria, etc.; the usual dose is 15 to 20 mins. thrice daily.

Quinidine. The physiological action of quinidine has been fully discussed under cinchona alkaloids. It has been employed in the treatment of persistent auricular fibrillation and flutter and also in paroxysmal tachycardia, in the intervals between the attacks. According to Lewis, it diminishes the sino-auricular rate, increases the refractory period of the auricular muscle and diminishes the rate of conduction of impulses along the A. V. bundle. General toxic symptoms, cardiac failure and embolism may occur during the administration of quinidine. Quinidine is contra-indicated in: (1) quinidine susceptibility, (2) arteriosclerosis, (3) failure of compensation, (4) cardiac dilatation and hypertrophy, (5) marked valvular disease, (6) a history of embolism, (7) heart block and (8) endocarditis.

A preliminary course of rest and of digitalis is advisable before administering quinidine. To obtain an effect on the heart the continued presence of the drug is necessary, and it should be given frequently. An average scheme for administration would be:—A test dose of 0.2 gm. (3 grains) is given and repeated in two hours. If there is no susceptibility to the drug,

begin the next morning with 0.2 gm. (3 grains) four to six times a day. If there is no effect in three days, the dose is raised. If the normal rhythm has not been restored by the end of the week, the drug will probably not prove successful. In some cases the test dose alone may bring the normal rhythm. If successful, the dosage should be gradually reduced and the patient kept on a daily maintenance dose for some time. The drug is usually given by mouth in capsules.

Glucose. It is a valuable agent in heart-failure. When given intravenously, after leeching or venesection, it acts as a food to the heart and stimulates the function of the kidneys. The details of therapy are given elsewhere.

Cane-sugar is considered to be a valuable cardiac nutrient. In the body, it is first converted into glycogen and thence to glucose, and as such serves as a source of food for the heart muscle in conditions of prolonged strain in some acute fevers, as pneumonia, influenza, typhoid as well as in cases of chronic cardiac failure. It is invaluable as a stimulant of body metabolism in various other morbid conditions, anaemia, a-dynamic varieties of rheumatism and in neurasthenic manifestations of the neurotics, where the metabolic processes of the body are depressed. The average adult dose for the sugar is 4-8 ounces a day.

Oxygen. It has been found very useful in cardiac disorders with hypertension, arteriosclerosis, aortic insufficiency, etc. It is administered in form of oxygen bath, 90° to 95°F. (32°—35°C). It lowers the blood pressure, and there is a coincident diminution in the size of the heart. These effects persist only a few hours after the first bath, but after 15 to 20 baths, very prolonged and even permanent physiological and therapeutic effects are obtained. They are contra-indicated where the blood pressure is much below normal, especially if associated with mitral defect and profound anaemia.

Morphine. In nocturnal dyspnoea in cardiac decompensation, morphine is given in sufficient doses to allow the patient to be comfortable. The resulting absolute bodily rest is a prerequisite to the effectiveness of cardiac stimulants. No other

remedy will thus alter the entire clinical picture of a dying case in a short space of time.

There are but two contra-indications to the administration of morphine: (1) Progressive failure of the respiratory centre, (2) Suffocative oedema of the lungs with purulent bronchitis.

Kidney disease is no bar to morphia, because mania, delirium and even convulsions of uræmic origin are often markedly relieved by morphine. Rarely, morphia may induce some cyanosis, but this is readily counteracted by the liberal and continuous inhalation of oxygen by a nasal catheter passed well back into the posterior nares. In fact, in the sudden crises of coronary thrombosis, morphia and oxygen are the two potent remedies, best administered simultaneously.

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PART II

HELMINTHIC DISEASES

CHAPTER I

GENERAL CONSIDERATION

Worms are the oldest recognised parasitic organisms which have seriously affected both man and domestic animals. From time immemorial, therefore, attempts have been made to eradicate them from the body by means of different drugs. In spite of this fact it is only lately that the study of anthelmintic drugs has been taken up on scientific lines. In view of the fact that a very high proportion of the human race and a still higher proportion of domestic animals suffer from parasitic infections, particularly in the tropics, and that many of these infections are often severely injurious to the host, much attention has lately been paid to this subject and a great advance has been made in this important field of therapeutics. In the past it has been taken for granted that because a remedy is active against one species of parasite it will be efficacious against others also. These parasites, however, belong to several widely separated zoological groups and differ greatly in their anatomy, physiology, habits and habitat. It is not reasonable, therefore, to expect that any one drug will be effective in anything like an equal degree against such widely different organisms. From the therapeutic point of view parasitic worms may be divided into two main groups.

(1) **Those which live in the gastro-intestinal tract.** Here it is desirable to give drugs which are absorbed as little as possible from the gut, thus ensuring their contact with the

For detailed information on this subject the reader is referred to "Anthelmintics and their uses" by Chopra and Chandler, 1928, from which this section is largely extracted by kind permission of the publishers, Messrs. William and Wilkins Co., Baltimore.

parasites in maximum concentration and at the same time exerting a minimum effect on the host. The drugs are given by the mouth and recently some have been introduced directly into the duodenum. Hookworms, roundworms (*ascaris*), and intestinal flukes are fairly susceptible to these drugs; tapeworms are moderately susceptible, and oxyuris, *strongyloides*, *trichostrongylus*, *trichuris* and others still hold out to a large extent against all efforts to dislodge them.

(2) **Those which live in the tissues of the body and cause somatic infections.** For these extra-intestinal parasites, readily absorbable drugs are given which are more toxic to the parasites than to the host. These drugs may be given by the mouth but are often administered by subcutaneous, intramuscular or intravenous injection. It is only in recent years that any headway has been made against such somatic infections and fairly effective remedies have been discovered for schistosomes, liver flukes, etc.

The word anthelmintic is derived from *anti*—against, and *helminthos*—worm; it is commonly applied to those drugs which expel worms from the gut but anthelmintics may be used against worms in the liver, bladder, connective tissue, etc. These remedies have been commonly but inaccurately divided into *vermicides* (*vermes cæders*) and *vermifuges* (*vermes fugare*). There is, however, no sharp line dividing vermicial and vermifugal drugs, as very often the same drug may have a vermicial and a vermifugal action according to the dose in which it is given. Some drugs such as santonin have an entirely vermifugal action as the parasites are expelled alive, while others like chenopodium are vermicial. Male fern is classed as a vermicide though the tapeworms expelled are often alive.

The qualifications requisite for an ideal anthelmintic are:

(1) It should be safe for the patient. It should be borne in mind that anthelmintic drugs, in general, are not toxic specifically to the worms alone, but in a greater or lesser degree, to all living cells; they may even be dangerous to the host. It is, therefore, advisable that a proper diagnosis be

made by microscopic examinations of the stool, urine, blood, etc., before they are prescribed.

(2) It should be effective in removing the particular kinds of parasites for which it is given. This depends on several factors such as location and species of parasite, the choice, dosage and purity of the drug used, the preliminary preparation of the patient, administration of a post-purgative, dietary measures, etc. In spite of every precaution there are no anthelmintic drugs which have a 100 per cent. efficacy in safe doses for any species of parasites. Fortunately it is not essential to remove all the parasites as unlike bacteria or protozoa, they do not, as a rule, multiply rapidly in the body. Expulsion of the majority of worms is usually sufficient to render the infection innocuous. It is well known that hookworm infection is practically universally present all over India but the incidence of parasites in certain parts is so low that no untoward effects are produced.

(3) Simplicity of administration. This is of little consequence in the treatment of individual cases, but when treatment has to be carried out in large labour forces it is of great importance, as it not only saves time and trouble but also expense.

(4) The treatment should not be unpleasant and it should have as little after effects as possible. This is of importance when treating labour forces, as labourers will not take a drug with an unpleasant taste or one which produces disagreeable effects.

5. The cost of the drug should not be high. No expensive preparation will succeed for use on a large scale as an anthelmintic, however effective it may be.

Method of administration. All drugs belonging to this group are toxic not only to the parasites, but to the host also. Certain precautions regarding diet, dosage and prevention of absorption of the drug are necessary to minimise toxic effects. Anthelmintic treatment consists of three stages:—

(1) **The preparation of the patient.** In the old days starvation of the patient and a preliminary purgative were considered essential, the idea being to get the alimentary canal as empty as possible so that the drug could come into intimate

contact with the parasites. Starvation has, however, a weakening effect on the patient and renders him more susceptible to the toxic action of the drugs; further, absorption is increased from the empty intestines. A liquid diet for 24 to 48 hours before treatment is usually preferred with a saline purgative the night before. The withholding of solid food leaves the intestine comparatively empty, so that the drug is less diluted and the preliminary purgative helps to clear away the coat of mucus which covers the parasites. The drug thus comes in contact with the parasites in as high a concentration as possible. Some of the recently introduced anthelmintic drugs, such as chenopodium and carbon tetrachloride, are not only quite as effective when given without preliminary starvation and purging, but preliminary fasting and purging considerably enhances their toxicity for the host. With most anthelmintics, except those used against the tapeworm, a light meal at noon on the day preceding the treatment, followed by a liquid diet consisting of milk or broth in the evening, a purgative at bed time and administration of the drug in the morning before any food is taken are all that is required. For tapeworm infection it is necessary that the drug should come into contact with the heads of the worms, otherwise the main body of the parasite is likely to break off leaving the head intact and in a few weeks the whole chain of segments is regenerated. The preliminary preparation is, therefore, essential here. Even with the most careful preparation the best remedies give only about 50 per cent. of cures and without preparation the hope of success is much reduced. *Strongyloides* or *trichostrongylus* are also deeply imbedded in the intestinal wall and the preparation for treatment of these infections has to be very thorough.

Absorbable fats are contraindicated with most of the anthelmintics used against the intestinal parasites, as their presence in the gut leads to absorption of these drugs. Many of the anthelmintic drugs, *e.g.*, carbon tetrachloride, thymol, are soluble in alcohol and its presence in the gastro-intestinal tract is liable to increase their absorption, thus producing toxic effects. It is best, therefore, to forbid its use. For remedies which act upon the liver (*e.g.*, carbon tetrachloride)

if this organ is well stocked with glycogen, it is relatively resistant and, therefore, a rich carbohydrate diet is indicated. In the case of drugs which are poisonous but very insoluble in water, *e.g.*, thymol, the amount of water consumed should be cut down to minimum to prevent their solution and absorption. On the other hand, with drugs which are largely absorbed, and excreted by the kidneys, *e.g.*, beta-naphthol, plenty of water should be given.

A limitation of protein diet is said to be harmful to the parasites. Some foods irritate the parasites but this hardly amounts to anthelmintic action. Mechanical irritation with fibrous vegetables, seeds of figs, strawberries, etc., and the husks of grain are said to have unfavourable effect on the worms. Condiments such as mustard, pepper, onion, garlic, spices, etc., were recommended in the olden days as accessories to anthelmintic treatment. Although *in vit* the anthelmintic power of drugs is enhanced by the presence of these substances, their value in the body is doubtful.

The selection of a preliminary purgative depends on the nature of the anthelmintic to be given. In the case of thymol and carbon tetrachloride, oily purgatives should be avoided because these drugs are soluble in fats and the chances of absorption are increased. Non-absorbable oils such as castor oil or paraffin oil are much less dangerous but even these are not recommended. In the case of drugs like chenopodium, oily purgatives can be advantageously used. Chenopodium oil is readily soluble in castor oil and since it is a local irritant its dilution in non-absorbable oils is advantageous in preventing it from coming in contact with the mucous membrane in concentration which will be injurious. Castor oil also neutralises the paralytic action of chenopodium on the intestinal wall. As a general rule, it is preferable to give saline purgatives because they do not increase the solubility of the drug, they create an osmotic pressure and a flow into the lumen of the gut, instead of away from it and lastly they tend to dissolve mucus and, therefore, expose the parasites to the action of the anthelmintic. Magnesium sulphate or sodium sulphate or a combination of

the two, in dose of one ounce of the saturated solution diluted to two or three ounces is recommended.

2. **The administration of the drug.** The method of administration is determined by the drug prescribed. Water-soluble drugs, if they have not a nauseating taste, may be given in water. Fat soluble drugs, like beta-naphthol and oil of chenopodium, if also water-soluble and absorbable, may be given dissolved in non-absorbable oils. Drugs which are poisonous after absorption in large quantities and which owe their safety to the fact that they are insoluble in water, *e.g.*, thymol, carbon tetrachloride, should under no circumstances be given with fats. It is always safer to avoid the use of oils entirely with male fern. Carbon tetrachloride is insoluble in water and is dangerous if dissolved in oil; it emulsifies when shaken vigorously with milk and the latter forms an excellent medium for its administration. Given in this way it becomes uniformly distributed in the stomach, and the burning sensation which it usually produces is reduced. For nauseating and objectionable-tasting drugs, *e.g.*, chenopodium, filix mas, etc., gelatine capsules are useful. Hard capsules should always be used since soft gelatine capsules do not dissolve in the upper part of the intestine where the action is desired. Soft capsules are best used in the case of worms residing in the lower portions of the gut, *e.g.*, oxyuris, trichuris.

Powdered drugs can be given in the form of powders, cachets or tablets and they are often combined with substances which aid their action, *e.g.*, santonin is combined with calomel. It is better to give some drugs such as oil of chenopodium, beta-naphthol, male fern, etc., in divided dose at intervals of half an hour to one hour as this insures a longer period of contact with the worms. Besides, if toxic symptoms are produced the next dose can be withheld. Division of doses is, however, disadvantageous when a large number of individuals have to be treated at one time. With drugs like carbon tetrachloride this method is contra-indicated as it is liable to promote absorption.

Anthelmintics in the form of enemata are given for parasites residing in the large intestines and many substances have been recommended for this purpose, *e.g.*, sodium chloride, quassia,

turpentine, etc. The enema should be injected as high up into the colon as possible because often the parasites such as oxyuris are situated in the cæcum and in the neighbourhood of ileo-cæcal valve. It should be preceded by a purgative and liquid diet the night before, and a preliminary washing out of the colon with soap and hot water on the morning of the treatment. Sometimes an anthelmintic given by the mouth is effective in this class of infection.

For parasites residing in the tissues, intravenous injections of drugs such as tartar emetic, emetine, etc., are desirable, or anthelmintics may be given by the mouth, *e.g.*, carbon tetrachloride for liver fluke infestations. For lung infestations drugs may be administered by inhalation.

3. **Expulsion of the worms and the toxic drugs.** A post-purgative may have to be used in the case of some of the anthelmintics as they merely stupefy or paralyse the worms or possibly merely irritate them and if they are not quickly swept out in this condition they may revive and obtain a fresh hold. A brisk purgative in these cases quickly washes them out from the intestines while they are still under the influence of the drug. Some purgatives have an irritating effect on the parasites and the increase of peristaltic movements also helps in removing the unattached parasites. Some anthelmintics have a purgative action of their own, *e.g.*, thymol, and with these, post-purgatives are not necessary though they are often administered. One great advantage of a post-purgative is that it hastens the elimination of the anthelmintic after it has acted on the worms, and in this way absorption and consequent toxic effects, if any, are prevented.

The time at which a post-purgative is given is determined by the location of the parasites, *e.g.*, for hookworms and ascaris situated in the upper portion of the gut it may be given simultaneously with the anthelmintic (which is an advantage especially in carrying out mass treatments) or very soon after. For tapeworms, situated lower down, the post-purgative is usually given one hour after; for oxyuris and trichuris an interval of two hours is necessary. It is often advisable to give another purgative on the second day of treatment, as it may eliminate

some of the worms which have succeeded in establishing themselves temporarily in an unfavourable situation lower down in the intestine.

Repetition of courses of treatment especially in case of the intestinal parasites, liver flukes, etc., should never be made in less than one to two weeks, to allow sufficient time for the repair of any damage to the host, caused by the first course. Besides it is seldom possible to be sure that the anthelmintic has failed, in less than a week or even longer. In the case of treatment of tapeworm infection, even when failure is established by unsuccessful search for the head, it is advisable to wait until the parasites have had time to grow again, since the weight of the paralysed or killed worm may draw the head away or may bring it into a position where it is exposed to action of the drug later on.

Criteria of cure. Disappearance of eggs or embryos in the faeces is the usual criterion of cure and is applicable to all intestinal and hepatic flukes and nematode infections except oxyuris. Eggs deposited in the gut prior to treatment may possibly appear in the stool for a few days afterwards. Carbon tetrachloride and some other anthelmintics also have a tendency to inhibit production of eggs for a time, without necessarily killing or expelling worms; in the case of carbon tetrachloride this inhibition may be exerted for as long as twelve days. A re-examination of the stool should be carried out after that period, though a positive examination between the third and twelfth day of treatment conclusively indicates failure. Delayed cures are also effected in the case of hookworm and possibly some of the other parasites; the eggs cease to appear and the worms are expelled a few weeks after the administration of the anthelmintic. This is due probably to the parasites being swept into unfavourable positions in the intestine where they persist for some time but eventually lose their hold and are expelled. It should also be borne in mind that reappearance of eggs two to three weeks after treatment, while it shows that a complete cure has not been effected, does not mean that the anthelmintic has proved entirely useless. In the case of hookworms intestinal anthelmin-

tics often cannot reach the young worms which are hidden in the folds of the mucous membrane or between the villi or which have not reached the alimentary tract. The young parasites and even some of the old ones (*e.g.*, strongyloides) may bury themselves in the mucosa, and may thus be out of reach of the drug.

In the case of oxyuris the search for eggs cannot be relied upon as a criterion of cure, since eggs are not consistently present in the stools but only when female worms become crushed or disintegrated. The entire stools should be searched for the adult living worms. Besides, reinfection not infrequently occurs and oxyuris found in the stools a few weeks after treatment does not necessarily mean that the anthelmintic was ineffective. In the case of tapeworm the criterion of cure depends on the species involved. The common tapeworm of man (*hymenolepis*) can be detected by searching for eggs, but it may be several weeks after treatment that the eggs reappear. This is due to the fact that even though the worms are not expelled the body is broken off just behind the head and it takes time for the segments to re-form. In the majority of tapeworm infections much reliance cannot be placed on searching for eggs; segments may be found in the stool but this takes time. In the case of the tæniæ also the body breaks off and it requires two to three months before the parasite matures and segments reappear.

In the case of schistosome infection, eggs do not always disappear from the urine and fæces immediately after clinical cure since antimony compounds are lethal both to the eggs as well as to the worms and the eggs which are passed subsequent to the destruction of the adult parasites are dead eggs. Their condition can be determined at once by examining them under the microscope or by the hatching test; this is carried out by washing them and putting them into water when the majority of viable eggs hatch out in a few hours and the liberated embryos can be seen swimming about. In the case of *Filaria bancrofti* it is not known how long the embryos circulate in the blood if the parent worms are dead; the criterion of cure has, therefore, to be worked out.

Choice of anthelmintic. Under ordinary circumstances when environmental conditions are not suitable for the transmission of intestinal parasites, helminthic infections are markedly reduced without any treatment whatsoever. The methods of disposal of human fæces are, therefore, more effective in the control of the common human intestinal parasites than the use of the anthelmintics alone. For curative treatment, however, drugs are necessary. The anthelmintic drugs can best be classified into two main groups:—

(1) Those which act on the cestodes or tapeworms; this is called the *cestode group*, e.g., aspidium, kousso, pomegranate bark, etc.

(2) Those which act on the nematodes, called the *nematode group*.

The trematodes come somewhere between the two so far as their reaction to anthelmintic drugs is concerned. They are susceptible to a greater or lesser extent to both groups and more so to those of the nematode group. Santonin, chenopodium, thymol, spigelia, azadirachta, etc., are effective against nematodes and flukes and they have a relatively low efficacy against tapeworms.

Other factors in the choice of an anthelmintic in the selected group must necessarily depend on the indications for, and contra-indications against its use, the particular kind of worm to be attacked, and convenience of administration. For example, carbon tetrachloride cannot be administered to people with cirrhotic livers, oil of chenopodium is contra-indicated for very young children or pregnant women, or beta-naphthol for people infected with malaria. Carbon tetrachloride is particularly effective against necators, less so against ankylostomes and oxyuris, still less against ascaris, and practically useless against strongyloides and trichuris. The oil of chenopodium is relatively more effective against both ankylostomes and ascaris than carbon tetrachloride; santonin is highly effective against ascaris but has no action on hookworms. It sometimes happens that one drug fails in an individual and another succeeds. Sometimes combinations of anthelmintics are of great value, for example, carbon tetrachloride and chenopodium

mixture ; the combination of these two drugs is more efficacious than either drug given alone, and it is possible to reduce the dose of each drug thus rendering them safer.

Effect of temperature. Rivas (1926) pointed out that both protozoan and metazoan intestinal parasites are killed in ten minutes by exposure to a temperature of 45°C. and in a few minutes by 47°C. He suggested intra-intestinal lavage with hot water for parasites living in the small intestine and colonic lavage for those residing in the colon. Hall and Shillinger (1926) experimented on dogs with water at temperatures of 47° to 48°C. administered in quantities of 2 to 4 gallons by means of a duodenal tube. They found that though 97.7 per cent. of ascaris and 77 per cent. of hookworms were removed the temperatures were too high to be safe and many animals died of gastro-enteritis and pulmonary congestion. With lower temperatures such as 40° to 45°C. the mortality was less but the treatment was not so effective. This treatment cannot, therefore, be recommended in human beings.

Experimental investigation of anthelmintic drugs. The experimental work is difficult owing to the impossibility of using artificially infected animals on a massive scale as can be done with protozoal diseases. The effect of anthelmintic drugs can be tested on parasites *in vitro*, but these parasites are difficult to obtain and to keep alive. Sollmann (1918) employed earthworms for testing the action of anthelmintic drugs *in vitro* and found that the drugs which are non-toxic to these worms are not likely to be active, while drugs which are lethal to them have possibilities of effective anthelmintic action. In some cases the toxicity to the earthworm runs parallel with their toxicity to parasitic worms, and a method of assaying these drugs with earthworms has been evolved. The worms are distributed into separate vessels containing carefully measured volumes of liquid; a different amount of the drug to be tested is put in each, except in one vessel which is kept as a control. The behaviour of the worm is then noted. Extreme restlessness or spastic contractions indicate irritation—possibly vermifugal activity. The time of death is noted and the results are compared with a similar series made with a standard preparation. Aspidium, chenopodium, santonin, spigelia, etc., can all be standardised by this method.

In vitro tests are, however, merely a preliminary step and must be followed by *in vivo* tests. In most cases dogs respond to anthelmintic drugs in much the same way as human beings though perhaps they are more resistant; they are, therefore, particularly suited for anthelmintic experimentation. As a rule with most of drugs known, a dog weighing 20 kilogrammes can be given the same dose as an average adult human being, but this may not be so in case of all drugs. The worms expelled by the drug are carefully counted and the results are

compared with the number of worms still present on post-mortem examination. Darling and Smillie's standard test treatment method is applicable to man. The drug is first given to a series of infected individuals and the worms which are expelled are carefully searched for and counted. Subsequently a full dose of an anthelmintic of known efficacy is administered, and the worms eliminated are compared with those expelled by the experimental drug. All these worm count methods are very laborious and they are not thoroughly reliable. The worms are mostly expelled in the first 18 hours after administration of the drug but elimination may continue for five days and, therefore, all stools during this period should be saved and examined; some worms may even be digested.

Another method of determining the efficacy of anthelmintic medication is by making differential egg-counts before and after the treatment. In the case of necators for example, the number of eggs produced by a female per day is fairly well known and the number of worms harboured can be roughly estimated by determining the average number of eggs per gram of faeces for a period of not less than three days. Such determinations made before the treatment and then a week or ten days after the treatment enable us to know the relative number of female worms eliminated. In most infections the number of males and females is roughly about equal.

Correlation between chemical composition and anthelmintic action of drugs. The study of the chemical constitution of the active principles isolated from drugs has led to the synthetic production of important compounds with marked physiological properties. Pharmacologists and chemists have been working together to find out what portion of the molecule is responsible for the physiological effects produced by a drug, and this has laid the foundation of the subject of correlation of chemical composition to physiological action of drugs. It is found that though in some cases a distinct relationship can be traced between these two, in the majority of cases the relationship is very obscure and difficult to understand. Very small changes in the chemical constitution completely change the physiological action of drugs, *e.g.*, cocaine has strong local anaesthetic action while alpharocaine has none; l-adrenalin is much more active than d-adrenalin. Changes in the chemical composition of compounds produce changes in their volatility, solubility, osmotic properties and diffusibility, and physiological properties are also altered.

The study of the relationship between the chemical constitution and the anthelmintic action of compounds was first taken up by Hall and Meyer Widgor (1917-18) but their work was interrupted by the War. Caius and Mhaskar made an elaborate study of a large number of anthelmintic drugs and attempted to correlate the efficiency of certain drugs with certain of their chemical constituents. Some very

remarkable facts have been brought to light in connection with the anthelmintic action and toxic effects of these drugs:--

(1) Hydrogenation of benzene lowers the toxicity towards the parasites but raises the toxicity towards the host as is the case with menthol.

(2) Total destruction of the benzenoid structure leads to the formation of non-anthelmintic toxic compounds.

(3) Esterification of the phenolic-hydroxyl group leads to the formation of non-anthelmintic non-toxic compounds, *e.g.*, thymotal.

(4) The mere presence of the phenolic-hydroxyl group does not always confer anthelmintic properties, *e.g.*, iso-amyl-phenol or iso-butyl-phenol which contain it are both inactive.

(5) The active anthelmintic principles in oil of chenopodium (paracymene, phellandrene, ascaridol) and thymol, contain free phenolic hydroxyl to which are attributed their anthelmintic properties.

(6) Methyl alkyl appears to intensify the anthelmintic action of phenolic-hydroxyl, *e.g.*, methyl-salicylate has marked anthelmintic properties while other salicylic acid compounds such as aspirin and salol are inert.

(7) Neither alcohol nor aldehyde groups have any anthelmintic properties.

(8) The anthelmintic activity of carbon compounds appears to be correlated with the chlorine content.

It will be seen, therefore, that in the majority of cases the relation between chemical constitution and their physiological action is not very clear. Change in chemical composition completely changes the physical properties of compounds. Their volatility, solubility, osmotic properties, ionisation, etc., undergo a complete change and so their absorption into the system and the physiological effects produced are also modified. In the present state of our knowledge of the changes going on inside the body of a living cell, it is impossible to speculate further.

INTESTINAL HELMINTHIASIS

In a general way parasitic worms fall into two groups as regards their reaction to anthelmintics; the nematodes and flukes respond to treatment with one group of drugs, which are classed here as the nematode group, whereas the tapeworms respond very feebly to these drugs, but are actively attacked by an entirely distinct group, which we therefore refer to as the cestode group. There are, however, some drugs which fall under both the groups.

1. Nematodes

Oxyuris vermicularis or threadworms. These parasites not only infest the colon and rectum but the upper portions of the gut as well. The treatment, therefore, consists of:—(1) The removal of the parasites and the eggs from the rectum and perineum. This is done by giving high and low enemas first daily and later bi-weekly or weekly. The patient should be put in knee-elbow position and large enemata of 1 to 2 quarts, of tepid or warm fluid are slowly given. The solutions used are 1, 2 or 3 per cent. sodium bicarbonate, sodium carbonate, sodium borate, or sodium chloride and as much as 1 to 2 pints (0.5 to 1 litre) or more may be given. Three to 4 ounces (90 to 120 c.cm.) of lime water are sometimes added to each injection, or 5 per cent. solution of boric acid may be given by itself. Soap water is a useful vehicle for oil of turpentine or oil of eucalyptus which are added in doses of 1 to 2 drachms (4 to 8 c.cm.) or more. The following are also used:—A decoction made from eucalyptus leaves; 20 drops of benzene added to 1 pint of warm water or soapsuds; a decoction made by boiling one ounce (30 gm.) of chips of quassia in 1½ pints (750 c.cm.) of water boiled down to a pint (500 c.cm.) and strained; 0.4 to 0.5 per cent. of quinine solution; 15 to 30 grains (1 to 2 gm.) of salicylic acid to a pint of water; ferric chloride 4 drachms (15 c.cm.) to a pint of water; ferrous sulphate 4 to 10 grains (0.2 to 0.6 gm.) in a pint; papain 10 to 20 grains (0.6 to 1.2 gm.) in a pint; hydrogen peroxide 1 in 5 to 1 in 10; vinegar diluted with 2 to 3 volumes of water; naphthalene 15 to 30 grains (1 to 2 gm.) in 100 c.cm. of water or 3 ounces of olive oil; tannin in the form of an infusion or decoction of krameria, logwood, catechu, kino and tincture of aloes (drachm to the pint).

In place of or following the enema, suppositories of ammoniated mercury, naphthalene, quinine sulphate or santonin may be employed. The perineum and anal folds (in females, the vulva and vagina) may be swabbed with 1 to 2 per cent. phenol and dusted with boric acid or 5 to 10 per cent. boric ointment employed to prevent reinfection.

To expel the parasites from the jejunum where they occur in large numbers, give calomel and sodium phosphate, or sodium sulphate or magnesium sulphate; santonin or thymol may also be given.

***Trichuris trichiura* or trichocephalus dispar or whipworms.** The measures used against threadworms are less effective against whipworms. The best drugs are:—Santonin and calomel gr. 2 to 3 each; oil of chenopodium 5 to 15 minims (0.3 to 1 c.cm) in the form of an emulsion; oleo-resin of aspidium; thymol 15 grains (1.0 gm.). The number of doses to be given depends on the effects produced on the patient. The drug should always be followed by a purgative. The stools must be repeatedly examined and treatment repeated until no parasites are found.

***Ascaris lumbricoides* or roundworm.** Infection with these parasites is very prevalent in many insanitary tropical countries and it is often associated with ankylostomes. They may give rise to intestinal obstruction, perforation of the intestines, intraperitoneal abscess, ileus and meningitic symptoms. The drugs commonly employed are santonin, oil of chenopodium and spigelia. Santonin and oil of chenopodium are usually effective. The day before the treatment a saline purgative such as sodium phosphate or sulphate or magnesium sulphate may be given. At bed time the bowel is washed with a soapsud enema. The following morning the anthelmintic is given in divided doses. Santonin usually combined with calomel is given at night followed by a saline the following morning. It is advisable to repeat the treatment after a week or two to make sure that all the worms have been expelled.

***Ankylostoma duodenale* and *necator americanus* (hookworms) and *strongyloides*.** Infestation with necators is common in Southern India; in northern parts of India ankylostoma is common; infections are generally of mixed types. Milder infestations such as those containing 100 to 500 eggs per gramme of faeces are harmless. Experienced workers say that about 100 worms are required to produce any pathogenic effects and 500 to 1,000 worms must be present for at least six months to produce well marked symptoms; 3,000 to 4,000 may be present

when severe degrees of anæmia exist. The other school holds that a small number of worms such as 10 or 20 may affect general health and working power, they therefore advise wholesale treatment. Infections are present both in tropical and subtropical zones all over the world. In India the heaviest infestations are found in places which experience heavy rainfall, e.g., Assam, Burma and Malabar, and moderate ones in Bengal, Behar, the United Provinces and the Southern Bombay coast. Eighty to 100 per cent. of infections occur in the country and 91 per cent. in the urban areas with an average only of 10 worms. Carbon tetrachloride, tetra-chlorethylene, thymol and chenopodium are given (see description of these drugs). After an interval of a month the stool should be examined and if ova are found the treatment is repeated.

Strongyloides often occurs in association with hookworms or independently; this infection is commoner in the Punjab and Rajputana. The females burrow into the intestinal wall and are difficult to dislodge.

II. Cestodes

A number of species of cestodes infest man, but only four are important: *Tænia saginata* or the beef tapeworm occurs all over the world. The heaviest incidence has been recorded in North China. *T. solium*, the armed or pork tapeworm enters the body through eating pork, the cysticercus stage (*C. cellulosæ*) being found in various parts of the body including the heart and brain. *Diphyllobothrium latum* or *Tænia lata*, is the broad or fish infesting tapeworm which causes profound debility and anæmia. It is a common infection in Canada and Northern Europe. *Hymenolepis nana* or *T. nana* is a small tapeworm occurring in man and rats in warm countries in many parts of the world. It is widespread in India. *H. diminuta* is another allied species. Prevention of infection in all cases should be attempted by thorough cooking of all contaminated meat; the food should be prevented from contamination by faeces of rats, mice, cats or dogs. Proper disposal of faeces is necessary to prevent spread of infestation.

The preliminary preparation of the patient in case of tapeworm infection must be thorough. The routine of treatment is described under aspidium. The patient should keep in bed after taking the drug. The stools should be passed in a chamber pot half full of water so that the worm can be recognised; this should be examined carefully to see if the head has been passed. In case the head is passed no more anthelmintic should be given but the stools should be watched to make sure that there is not a multiple infestation. If only segments have been passed the treatment should be repeated in full after 10 to 14 days. If there is doubt about the expulsion of the head, it is best to wait for 8 to 10 weeks, watching the stool in the meanwhile for reappearance of segments. If no ova or segments can be detected the head has been expelled. If *T. solium* is found, prompt treatment should be given since there is danger of cysticercus infection.

The cestode group of anthelmintics includes the phloroglucinol series, *i.e.*, male fern which is entirely successful in dwarf tapeworms, and also kousso and kaimala; pomegranate bark or its active principle pelletierine which should be employed when male fern fails; the active principles of areca nut (arecoline); peeps or pumpkin seeds are remedies against *T. saginata*. Other less important agents are cocoanut, butyl-chloral hydrate, oil of turpentine, brayera, etc.

CHAPTER II

ANTHELMINTICS ACTING ON CESTODES

MALE FERN AND ALLIED DRUGS

Male fern, Koussou and Kamala are the three important drugs included in this group. All these drugs, though derived from different sources are intimately related to each other from a chemical as well as from a pharmacological point of view. The active principles in all are chemically allied bodies, *i.e.*, derivatives of phloroglucin.

ASPIDIUM (MALE FERN)

Synonyms :—*Stipides aspidii*, *Radix Filicis Maris*, Sweet brake.

This is one of the oldest anthelmintic drugs known and was used by the ancient physicians, Pliny and Galen. *Aspidium filix mas* and *Aspidium marginale* are the two well-known varieties of ferns which are recognised in the British and United States Pharmacopœias. They both contain the same active principles, but the former yields smaller quantities of the rhizome. Several other ferns such as *A. spinulosum* and *A. dilatatum* growing in Europe and *A. anthelminticum* growing in South America contain similar active principles and properties. The rhizome and stipes of *Dryopteris filix mas* (Linn.) Schott (Fam. Polypodiaceæ) are chiefly used.

Chemical composition. The chemical nature of different constituents of the rhizome is not quite clear. This is due to the fact that most of the compounds are unstable bodies and undergo chemical changes even in the dry rhizome. The active principles are a number of non-nitrogenous substances the more important of which are as follows :—*filmaron* 5 per cent., *filicic acid* 2 to 4 per cent., and smaller quantities of aspidin, aspidinol and filicic acid. In addition there are tannic acid 10 per cent.; inactive filicic anhydride (filicin) produced in old specimens by transformation of filicic acid, 19 to 31 per cent.; a green fixed oil 6 to 7 per cent.; a volatile oil 0.02 to 0.04 per cent.; an uncrystallisable sugar, 11 per cent.; resin, starch, and wax.

The active substances are compounds of butyric and isobutyric acids with phloroglucin and its homologues. They are insoluble in water and soluble in fats and oils. The essential oil is light yellow in colour and gives it its peculiar odour. The poor absorption from the gut is dependent on the insolubility of the active principles in water.

Filicic acid or *filicin* occurs in two forms, (1) a crystalline inactive form and (2) an amorphous form which is said to be mainly responsible for the therapeutic activity of the drug. The crystalline form is the lactone of the active amorphous form and the latter readily changes into the former. This is the reason why the rhizome and its preparations deteriorate so quickly.

Pharmacological action. Straub has shown that the active principles of male fern are powerful poisons to smooth muscle and they also attack striated muscle. This quality of the drug probably accounts for its vermifugal action on the tapeworm. *In vitro* experiments show that non-striated muscle of invertebrates such as molluscs, annelids, echinoderms, crustaceans, etc., is very sensitive to filicic acid bodies and is rapidly paralysed by its direct action on the muscle fibres.

Internally, filicic acid has a strongly irritant action on the gastrointestinal tract and may produce vomiting and blood-stained diarrhoea, and in excessive doses collapse and death. The irritation of the gastrointestinal tract sets up reflex uterine contractions. It should not, therefore, be given to pregnant women. The liver is affected even after moderate dose producing bilirubinæmia, large doses may produce jaundice and cirrhosis of the liver. The heart muscle is depressed and the beats are slowed and weakened. The spinal cord is stimulated, at first producing twitchings and with large doses convulsions occur; later, ascending paralysis of the spinal cord sets in, and death occurs from failure of the respiratory centre. Small amounts of the active principles are absorbed from the gut and filicic acid and its decomposition products are excreted by the kidneys.

Principles of administration of *Filix Mas*. The fresh ethereal extract is usually administered in dosage of 10 to 30 minims every half an hour in capsules till the full dose is given; a grain of calomel may be added to each capsule. It may also be given in an ounce of milk with the yolk of an egg or some flavouring agent such as cinnamon oil or chloroform water, to conceal its nauseating taste. Two to 10 minims (0.1 to 0.6 c.cm.) of chloroform are said to enhance its efficacy. The oleoresin is given in a 30-grain dose (2 gm.) to an adult and $7\frac{1}{2}$ to 15 grains (0.5 to 1.0 gm.) for a child. It is best given in divided doses 10 to 30 minutes apart, the last dose being followed in $\frac{1}{2}$ to 1 hour by a full dose of magnesium

sulphate. Pills coated with keratin are preferred by some. Clayton Lane and Low recommend the following method of administration of the drug: liquid diet for two days; calomel or a saline purge in the afternoon of the second day; a cup of black coffee the next morning (third day); then one capsule containing 30 minims of the liquid extract at intervals of $\frac{1}{2}$ hour till three such are given. A drachm of brandy with 15 minims (1.0 c.c.) of chloroform may be given with the first dose, to prevent vomiting. A saline aperient (Epsom salts, Carlsbad salts or sodium sulphate) is given two hours after the last dose, to wash out the parasites and the drug.

In treating cases with the extract of male fern, three things are essential: (1) The alimentary canal should be properly prepared for the reception of the drug. The head of the parasite is imbedded in the intestinal mucosa between the villi, and unless the bowel is empty the drug does not reach it. (2) The extract, if used, should be fresh. This is important as the power of the extract to retain its potency is uncertain. The active principles of filix mas are easily destroyed and it has been noticed by several observers that the dried rhizome of the male fern gradually loses its activity on keeping. The extract should be made from specimens that have not been kept for more than a year. (3) The post-purgative given should be a powerful one, so that the head of the worm loses its hold and is expelled from the intestine.

All stools passed for 24 hours after treatment should be saved and passed through a fine sieve to search for the presence of the scolex or the head. If the head is not found, cure has not been effected and another course of treatment will be necessary. In such cases, treatment might be repeated after an interval of 10 to 15 days following the first course, as the drug undoubtedly has a cumulative toxic effect. The possibility of there being more than one worm should be borne in mind and this can be usually determined by piecing together the expelled segments.

Anthelmintic effects. The older physicians used this drug against all forms of helminthic infections, but recent work has

shown that it has little value against ascaris, hookworms and other nematodes. Against whipworms (*trichuris*) a small dose of the extract ($1\frac{1}{2}$ drachm) daily 2 to 3 days in succession and repeated after an interval of 10 days is effective. It is useless in schistosomiasis, somatic *tæniasis*, etc., although the drug is said to have some effect against liver flukes. On the cestodes the drug has almost a specific effect though failures are not uncommon. The failures recorded are mostly due to the poor quality of the drug obtained from the market and the careless preparation of the patient. Rarely, the parasites themselves show extraordinary resistance to the drug and cannot be expelled even after 5 or 6 treatments.

In Europe and America, *filix mas* is commonly used against *tænia* or *diphyllbothrium*. If the patients are properly prepared according to Lane and Low's method, 50 per cent. of cases of *Tænia saginata* infections are cured with a single treatment. It acts on *Hymenolepis nana* as well as the large *tæniæ*s, but as the former are small and are embedded in the mucus it is difficult for the drug to reach them. The rarer tapeworms of man, e.g., *Dipylidium caninum*, *Hymenolepis diminuta* and *Bertiella satyri* which are not normal human parasites, are more easily expelled than the species which have adapted themselves to the human host.

Signs and symptoms of poisoning. Male fern was formerly considered to be a harmless drug in man but recent experience has shown that it is very toxic and deaths have been reported from its use. Toxic doses vary within wide limits depending on the active principles present and also on the resistance of the patient. Anæmia, debility, old age and infancy are predisposing factors to poisoning. The presence of fatty substances in the gut increases absorption. Toxic symptoms are likely to occur after 2 to $2\frac{1}{2}$ drachms (8 to 10 gm.) of the extract, but severe poisoning has occurred after 1 drachm (4 gm.) given in a day. More than 2 drachms should never be given in 24 hours.

The chief symptoms in these cases are headache, vertigo and bilirubinæmia; slight jaundice frequently occurs. In moderately severe doses the symptoms are those of gastro-en-

teritis, *e.g.*, vomiting, abdominal pain, blood-stained diarrhoea ; headache, dizziness, shortness of breath, dimness of vision or yellow vision and sometimes amblyopia may be present. The patient becomes dyspnoëic, looks drowsy and feeble. The kidneys are irritated and albumin is often present in the urine. Hæmoglobinuria and hæmaturia rarely occur. In very severe cases the patient becomes delirious, gets severe cramps and violent convulsions ; he loses consciousness, respiration becomes slow and shallow, the pulse weak and imperceptible and there is marked cyanosis. Convulsions are followed by muscular relaxation, immobility of pupil, and abolition of reflexes are common. Optic neuritis resulting in temporary or even permanent blindness has been observed. Death occurs from respiratory failure or paralysis of the heart.

Treatment of poisoning. In treating cases of male fern poisoning, the stomach and the intestines should be evacuated at once. A quickly acting purgative such as magnesium sulphate or citrate may be given at once. Such purgatives as castor oil or croton oil should be avoided. Demulcent drinks should be given if diarrhoea and vomiting are present. The patient should be kept strictly in a recumbent posture, for there is danger of cardiac failure, and he should be kept warm. Cardiac stimulants, such as aromatic spirit of ammonia, spirit of ether or camphorated oil should be administered. If collapse occurs, give injections of pituitrin, adrenalin or ephedrine. Convulsions if present should be controlled by inhalation of chloroform or ether ; bromides may be given. If paralysis is present, give atropine or strychnine. Alkalies may be administered if hæmaturia is present.

Precautions and contra-indications. Preliminary preparatory measures should not be carried to extremes and starvation is not indicated ; the patient should be given a light diet and a preliminary purge. The administration of the extract should be followed up by a strong active purgative, so that it is eliminated from the gut without delay. Under no circumstances oily cathartics like castor oil, which facilitate absorption of the drug, should be given, for in 57 per cent. of cases severe poisoning has occurred subsequent to its administration. Other

solvents such as fats and alcohol should be avoided. A rapidly acting purgative such as magnesium sulphate, should be administered. Compound jalap powder, senna or calomel may be given previously or along with the drug. Weak and emaciated patients are not suitable cases for the administration of the drug. The drug is contra-indicated when ulceration of the stomach and duodenum is present because of its irritant action and the liability of greater absorption from the ulcerated surface. It should also not be given in pregnancy, affections of the heart, liver and kidneys.

Preparations.

Extractum filicis liquidum (B. P.) is prepared by ether extraction and contains not less than 20 per cent. of filicin. Dose 45 to 90 minims (3 to 6 c.cm.); as much as 2 drachms may be given. The extract loses its activity on keeping. The specimen of a good active extract is dark green in colour, while an extract which has turned brownish yellow and has a crystalline deposit at the bottom has deteriorated. As the extract has a very disagreeable taste and smell it is often given in capsules containing 15 minims each. Yeo gives capsules with one grain of calomel each. **Haustus filicis liq.** is in use in many hospitals. It consists of liquid extract of filix mas one drachm, syrup of ginger one drachm, tincture of quillaia $\frac{1}{2}$ drachm and peppermint water up to one ounce.

Oleoresina aspidium (U.S.P.) made by percolation with ether, is a solid substance and does not deteriorate so rapidly as the liquid extract. Dose 30 grains (2.0 gm.) once a day.

Filmaron is soluble in ether, alkali, and sparingly in alcohol. Dose 10 to 15 grains (0.6 to 1.0 gm.).

Amorphous fillic acid. Dose 8 to 15 grains (0.5 to 1.0 gm.) in a capsule.

KOUSSO OR CUSSO

Koussou is the dried female flowers of *Hagenia abyssinica* also known as *Brayera anthelmintica*, family Rosaceæ. The plant grows in north-eastern part of Africa and is cultivated in Abyssinia. It has been used as an anthelmintic from very ancient times. The entire panicles of the pistillate flowers collected after pollination, and dried in the Sun are most suitable for vermifugal purposes. Only the panicles are official in the pharmacopœia. Koussou has no odour but has a bitter acrid

taste. The drug loses its activity by ageing and, therefore, should be used as fresh as possible.

Chemical composition. Koussou is composed of two distinct parts: (1) the glands of the flower panicles containing the active principles and (2) sharp microscopic hairs which are mechanically irritating to worms and to the gut. The active constituent of koussou is *kosotoxin* which is a pale yellow, amorphous powder, insoluble in water but soluble in alcohol and ether; it melts at 80°C. By caustic alkalies it is converted into *kosin* or *koussein* (brayerin) which occurs in yellow rhombic crystals insoluble in water but soluble in alcohol, ether, and benzene and has a bitter acrid taste. Besides these it contains a volatile oil, resin, tannic acid, oil and gum. The commercial *koussein* is a mixture of various principles. By the action of zinc dust and sodium hydroxide *kosin* is split up into isobutyric acid and phloroglucinol which brings it closer chemically to anthelmintic ferns.

Pharmacological action. Kosotoxin is a protoplasmic poison. In frogs it acts like curare and paralyses the motor nerve endings of the striped muscle and finally the heart. In mammals, it stimulates the medullary centres. Both tapeworms and ascaris die when exposed for 30 minutes to an infusion of koussou.

Therapeutic uses. Koussou is used as a tæniafuge and is said to be the safest among this class of drugs. Its efficacy depends on its freshness. It is equally effective against all species of tapeworms and has also been used against ascaris. Koussein in small doses is preferable to other preparations. Usually 15 to 60 grains (1 to 4 gm.) are given in a capsule in divided doses hourly or half hourly, in much the same way as the oleoresin of male fern. The last dose is followed by a purgative. The usual dose for an adult is 2 to 4 drachms (4 to 8 gm.) of the powdered flowers. No fasting on the previous day is necessary. The drug is given in the morning on an empty stomach after the bowels have been moved, and no food except clear soup or weak tea are given till the worms are expelled. The infusion may be given in doses of 8 ounces (250 c.cm.) at once, or divided into 2 or 3 portions. As a rule, no after purgative is necessary, but if the bowels do not move a saline purgative should be given. Koussou is both a tæniacide and a tæniafuge, the latter property is dependent partly on the purgative action of the active principle and partly on the numerous fine pointed hairs which irritate the worm and drive it out.

Toxic effects. Kosotoxin is a toxic drug, 1 mgm. being fatal in a frog and 50 mgm. per kilo. in rabbits, dogs and cats. The lethal dose in man is not known. Moderately large doses produce nausea, vomiting and faintness; purgation usually begins after an hour. Larger doses produce gastro-intestinal irritation with continued vomiting and violent purgation. If the drug is absorbed there is headache, vertigo, mental disturbance, precordial pain, dyspnoea, painful micturition and sometimes convulsions.

Koussou and its preparations are contra-indicated in pregnancy, debility, and organic diseases of the heart and kidneys.

Preparations.

Powdered dried panicles of the pistillate flower is given in doses of 2 to 4 drachms (8 to 16 gm.).

Kosin (N. O.) is a yellowish bitter crystalline mass. Dose 7 to 15 grains (0.45 to 1.0 gm.) repeated every half hour till 4 doses have been given; last dose followed by a purgative.

Infusion brayeræ or infusion of koussou is prepared by pouring 1,000 c.cm. of boiling water over 50 gm. of powdered braver and allowing it to stand till cool. It is given without straining. Dose 6 to 10 ounces (190 to 300 c.cm.).

KAMALA

Synonyms:—Rottlerin, Kameela, Reroo

Kamala is a purplish-red or brick-red powder derived from the glands and hair of the fruit of *Mallotus philippinensis*, an evergreen tree belonging to the Euphorbiaceæ or spurge family. It has long been used as a tæniacide in India and at one time had gained a considerable reputation as an anthelmintic and was included in the British and United States Pharmacopœias. Further experience, however, showed that its action was uncertain and it was, therefore, discarded.

Active principles consist of:—(1) a brownish-red resin or resinoid *rottlerin* (mallotoxin) which can be easily converted into methyl phloroglucin. It is probably the same as *kamaline*. (2) *Iso-rottlerin* is probably impure rottlerin. Besides these, there are resins, starch, traces of a volatile oil, oxalic and citric acids. Powdered kamala is given in doses of 2 to 8 drachms mixed with milk, curds or honey. The drug met with on the market is often adulterated with ferruginous sand, red brick dust, ferric oxide, dyed starch. etc.

Action and uses. The drug irritates the gastro-intestinal tract and even in therapeutic doses produces considerable nausea and increase of peristaltic movements of the gut. It has thus a purgative action. Large doses produce gastro-intestinal irritation and set up vomiting and violent purging.

The chief advantage of this drug appears to be that it can be safely given without any preliminary preparation of the patient; no post-purgative is necessary. It is much less efficient against tapeworm than male fern. It is useless against hookworm, ascaris and whipworm. It is a mild drug and is only indicated in children and debilitated individuals in whom extract of filix mas is not advisable.

Kamala is also applied externally in 10 per cent. lotion and ointment for scabies and other parasitic affections of the skin.

OTHER ANTHELMINTICS

Pomegranate or granatum. The bark of the pomegranate tree, *Punica granatum* Linn. (N. O. Lythraceæ), has been employed as an anthelmintic in India from time immemorial and was used by the Romans. Both the root bark and the stem bark have been used but root bark is preferable inasmuch as the alkaloidal content is greater than that of the stem bark.

Chemical composition. The active principles of the bark are 4 alkaloids: (1) *Pelletierine* or *punicine*, the most important of the group, is a colourless volatile liquid which turns dark on exposure. It has a boiling point of 195°C. (2) *Iso-pelletierine*. Only these two alkaloids are supposed to possess activity against tapeworms. (3) *Methyl-pelletierine* closely resembles pelletierine and (4) *Pseudo-pelletierine* also known as *methyl granatine*. The last two alkaloids are inactive. The mixed alkaloids were put on the market under the name of pelletierine (the names punicine, isopunicine, etc., have been adopted for the pure alkaloids). The bark also contains *puni-cotannic acid* which has a tæniacidal action, and it renders the alkaloids insoluble and prevents their absorption from the gut. The sulphates of the alkaloids are soluble and are readily absorbed. This explains why the bark is a better anthelmintic.

Pharmacological action. The alkaloids pelletierine and iso-pelletierine have a local irritant action and even in small doses they produce vomiting and colicky diarrhoea. They are absorbed from the gut if given in soluble form and are readily destroyed in the body. They act on the nervous system producing headache, vertigo, drowsiness, ocular disturbances and dimness of vision. Toxic doses have a paralyzing effect on the motor nerve endings and give rise to numbness and cramps of the lower extremities, paralysis of the diaphragm and convulsions from asphyxia. In rabbits there is progressive mus-

cular paralysis. Unstriated muscle fibres are first stimulated then paralysed. *Tænia saginata* which usually live for hours in a solution of sodium chloride kept at body temperature, are killed in about 10 minutes if 0.01 per cent. pelletierine is added to the solution.

Anthelmintic use. The fresh bark is said to be a fairly good anthelmintic against tapeworms. The bark is, however, unpleasant to take and on account of the large quantities of tannic acid present it is liable to produce nausea and vomiting. Experience shows that it is also uncertain in its action. Pelletierine in the form of tannate given in doses of 2 to 8 grains (0.12 to 0.5 gm.) acts as an excellent tæniacide without producing marked toxic effects. The soluble salts are absorbed and produce toxic effects. Absorption is favoured by alcohol, and for this reason fluid extract is not such a good tæniafuge as the decoction or powdered bark. If the preliminary preparation of the patient by dieting and purging is carefully attended to in the same way as with aspidium, pelletierine tannate will seldom fail to produce an efficient vermifugal action. After liquid diet for two days and a strong preliminary saline purgative the night before treatment, pelletierine is given in the morning in sweetened water followed by a brisk saline cathartic half an hour later. The patient should stay in bed after taking the medicine as dizziness is always experienced. The worms are expelled 2 to 4 hours later. This drug ranks next only to *filiæ mas* as a tæniacide, and is specially recommended against infestations with *Tænia solium*. Against *Hymenolepis nana* it is not effective.

Toxic effects. Large doses of the decoction or the alkaloids produce headache, dizziness, dim vision, nausea, vomiting, diarrhoea, weakness of the limbs followed by paralysis. Drowsiness and coma may supervene. Serious disturbances in the eyeball such as dilatation of the pupil, retinal congestion and amaurosis may occasionally occur.

Treatment of poisoning. Treatment is largely symptomatic; rapid emptying of the bowels, administration of stimulants and artificial respiration when the respiratory muscles are affected, are important. A brisk purgative such as calomel and saline should be given immediately. If the patient is seen soon after ingestion of a large amount of the drug, gastric lavage is indicated. Demulcent drinks to soothe the gastro-intestinal irritation are recommended. Tannic acid may be given. Stimulants such as strychnine are indicated.

Preparations.

The dried powdered bark is given in doses of 20 to 40 grains (1.3 to 2.0 gm.).

Granati (U.S.P.X.) is prepared by exhausting the powdered bark with 37 per cent. alcohol and 10 per cent. glycerine. Each c.cm. represents 1.0 gm. of the drug.

Pelletierine (mixture of the alkaloids), dose 2 to 6 grains. **Ext. Granati Liq.**, dose 30 to 120 minims. **Pelletierine sulphate**, dose 2 to 3

grains. **Pelletierine tannate** (B. P.) is a yellow, amorphous powder, dose 2 to 8 grains. **Pelletierine hydrobromide** is a brownish viscid liquid, dose 2 to 8 minims.

Areca nut. Synonyms:—*Arecae semina*, betel nut. Areca nut is the seed of *Areca catechu* belonging to the family *Palmaceae*. It has been used for a long time in India and China as an anthelmintic both for man and animals and was considered so effective that it was included in the British Pharmacopoeia. Recent work has thrown considerable doubt on its anthelmintic value.

Chemical composition. Several alkaloids have been isolated from the seeds which are all chemically related to each other. These are, *arecoline* and *arecaine* which occur in the same proportions (0.1 per cent.), *arecaldine* and *guvacine* occur only in traces. *Arecoline*, a colourless oily liquid is physiologically active; the other three are probably inactive. To it the anthelmintic and sialogogue properties are mainly to be attributed. There is also an essential oil (which contains laurin and myristin), several sugars, iron, magnesium and other salts.

Pharmacological action of arecoline. Arecoline base is not soluble in water and is not readily absorbed; the soluble salts of arecoline are rapidly taken up from all mucous membranes and poisoning can be produced by instilling a 1.0 per cent. solution into the eye. It is excreted unchanged in the urine. The action of arecoline resembles that of pilocarpine and physostigmine and is chiefly on the autonomic and central nervous systems. It stimulates the nerve endings of the plain muscles and glands; there is inhibition of the heart and fall of blood pressure, constriction of the pupil, contraction of the bronchial musculature and definite increase of the peristaltic movements of the intestine owing to stimulation of Auerbach's plexus; the flow of saliva and sweat is stimulated. In the heart the entire intra-cardiac inhibitory nerves are stimulated and the heart, whether intact or isolated, stops in diastole. The blood vessels are not affected and the blood pressure falls owing to the action of the drug on the heart. The spinal cord is at first stimulated and then paralysed; the respiratory centre is depressed and the vagus centre is stimulated. In frogs convulsions resembling those by strychnine are produced; the heart becomes slowed and finally stops in diastole. In cats and dogs there is profuse salivation, vomiting, diarrhoea, increase of spinal reflexes and tetanic convulsions. Tapeworms and liver flukes placed in dilute solutions of arecoline salts are rapidly paralysed.

Anthelmintic uses. Areca nut is not an effective drug against nematodes and its efficacy against tapeworms and flukes is doubtful. The powdered nut in doses of 1 to 3 drachms (4 to 12 gm.) is given in syrup. It has undoubtedly an irritant action on the gut and produces purgation, but it does not expel worms. Arecoline salts are given by the mouth in man in doses of 1/15 to 1/10 grain (4 to 6 mgm.) or

subcutaneously $\frac{1}{4}$ of the amount. One to 2 grains are given to cattle to relieve colic.

Toxic effects. Arecoline in pure condition is a toxic drug. As it is readily absorbed from the gastro-intestinal tract it is considered dangerous for use as a tæniacide. Arecoline poisoning, however, might occur when large doses of the powdered nuts are administered. The symptoms resemble those of fungus poisoning (muscarine) and consist of vomiting, diarrhoea, colicky pains, marked salivation, laboured breathing, tremors, convulsions, coma and death. If toxic symptoms supervene, rapid evacuation of the bowels and administration of cardiac and respiratory stimulants are indicated.

Preparations.

Dry and fresh powdered seeds, dose 1 to 3 drachms (4 to 12 gm.).

Arecoline dihydrobromide and dihydrochloride occur in white crystals soluble in alcohol and in water. It is official in some of the pharmacopias, dose 1/120 to 1/40 grain.

Pepo. Pumpkin seeds. The seeds of *Cucurbita pepo* and *C. maxima* (melon pumpkin) have been used for ages as a household remedy against tapeworms. They are said to have succeeded when other drugs have failed. It is difficult to say how the anthelmintic action is produced. There are no active principles, as far as is known, and the therapeutic activity, if any, is probably due to mechanical action of the sharp edges of the bruised seeds.

Chemical composition. *C. pepo* contains 40 per cent. of a fixed oil and 30 per cent. of starch, a soft bitter acrid resin which is said to be the active constituent, a volatile oil, and 30 per cent. of starch, sugars and proteins. *C. maxima* contains 30 per cent. of a fixed oil and an acid resin, which was supposed to be responsible for the anthelmintic activity of the seeds but later proved to be useless.

Pharmacological action. *Ascaris*, *Tænia saginata* and *Diphyllobothrium latum* are said to be irritated and dislodged by the husks and paralysed by the oil and resin. *Tænia solium* and *Hymenolepis nana* are apparently more resistant. *In vitro* studies by Power and Sollmann have shown no destructive action. Neither the seeds nor the oil have any marked physiological activity.

Anthelmintic effects. The seeds administered should be fresh, certainly not more than a month old. Two to four ounces are administered crushed or beaten into a paste with water and finely divided sugar, the whole being made up to one pint. Sometimes a little milk is added. The usual preparatory dietetic measures are carried out and a saline purgative is given the night before and again early the following morning. A very light breakfast is taken and two hours later the seeds are given in three portions, 2 hours apart. The patient should

remain in bed. If effective purgation does not occur within 3 hours of administration a dose of castor oil should be given. Experiments recently carried out on dogs to test the anthelmintic effects of the seeds gave inconclusive results. The seeds are sometimes taken three or four times a day for a few days until the worms are expelled. No toxic symptoms are produced even after large doses. Pumpkin seeds are used with great confidence by many physicians against tapeworms especially in the very young or aged, debilitated persons, and pregnant women. They are not so effective against the armed and dwarf tapeworms. Roundworms are also expelled. Pumpkin seeds are indicated in those cases of infestation where male fern, kousso, santonin, etc., are contra-indicated. Oil of pumpkin seeds is sometimes used instead of the seed but it is less effective.

Preparations.

Cucurbita semina præparata (B. P.). Dose 1 to 2 ounces (30 to 60 gm.) or more. **Oleum peponis** (N. O.) obtained by extraction with acetone, is a thick reddish-brown liquid. Dose $\frac{1}{2}$ to 1 ounce (15 to 30 gm.).

Cocoanut. The flesh and milk of the cocoanut, the fruit of a palm *Cocos nucifera* are said to have anthelmintic properties and to be specially effective against tapeworms. They have been largely used in India and other Eastern countries. When ingested in large quantities, the milk and the meat have a purgative action and are said to expel not only the worm but its head also. This, however, is doubtful. The patient usually fasts for 24 hours, drinks the milk and eats the meat of one whole nut; 2 to 3 hours later a purgative is given.

Musenno. The bark of *Acacia anthelmintica* or *Albizzia anthelmintica*, an Abyssinian tree belonging to N. O. Leguminosæ, is used as a tæniacide in Abyssinia. The bark is sold in flat pieces 5 to 10 inches long and is pale yellow in colour. It has an acrid taste and contains resins, an amorphous saponin-like principle *musennin* and an alkaloid *moussennine*. Two to four ounces of the powdered bark suspended in water or mixed with flour in the form of bread, or made into an electuary with honey are taken in the morning before breakfast. In Western medicine musenna is used in the form of an infusion in doses of 1 to 6 ounces, given in several portions and followed by a purgative. Moussennine has been isolated and given in doses of 3 to 4 grains (0.2 to 0.25 gm.).

Carbon tetrachloride. It has been shown to be an effective anthelmintic against tænia infections. See under carbon-tetrachloride.

CHAPTER III

ANTHELMINTICS ACTING ON NEMATODES

CARBON DERIVATIVES

This series of compounds is composed mainly of carbon and halogens. It was first suggested by Caius and Mhaskar that anthelmintic activity is correlated with the chlorine content and since chloroform shows a considerable anthelmintic efficacy against hookworm, some of the related compounds with higher halogen content may prove even more effective. Working on this hypothesis Hall (1925) tried carbon tetrachloride (CCl_4) as an anthelmintic with excellent results. Carbon tetrachloride has a marked anthelmintic effect against hookworms and its toxicity to animals is not very great. Owing to its low solubility and volatility and consequent slow rate of diffusion, comparatively small quantities are absorbed into the circulation. Large quantities can, therefore, be introduced into the alimentary canal without untoward effects. Other compounds related to carbon tetrachloride have also been tried. Ethylene dichloride or dichlorethylene ($\text{C}_2\text{H}_2\text{Cl}_2$) has been shown to be an effective anthelmintic against hookworms but it is distinctly weaker than chloroform and carbon tetrachloride; tetrachlor-ethylene (C_2Cl_4) is as effective against hookworms as carbon tetrachloride. Carbon trichloride or hexachlor-ethane (C_2Cl_6) is another of these compounds which has been tested but found ineffective. It is difficult to say, which are the factors responsible for the anthelmintic properties of these compounds. The chlorine content or chlorine concentration has been suggested as the explanation but a close study of the properties of these compounds seems to point to the physical factor of solubility.

CARBON TETRACHLORIDE

Carbon tetrachloride was discovered as long ago as 1849. It is chemically related to chloroform and this led Simpson

to try it as a general anaesthetic, but it was later on discarded because it failed to show satisfactory results. Hall (1921) found that it removed 100 per cent. of hookworms in dogs and recommended its trial in human beings. The drug is well tolerated in such doses as 4 to 6 c.cm., the only symptoms noticeable occasionally being dizziness, abdominal distress and vomiting. Further work has demonstrated beyond doubt the great efficacy of this drug in the treatment of hookworm infestations in man.

Chemistry and properties. Carbon tetrachloride is prepared from carbon bisulphide by direct chlorination in the presence of a catalyst such as aluminium chloride. It is also prepared by heating chloroform with iodine chloride at 165°C. when it is obtained free from contamination with sulphur compounds. It is a colourless non-inflammable liquid, having a disagreeable penetrating odour. Its specific gravity is 1.6, its molecular weight 153.8, and its melting point is -22.9°C., boiling point 77° to 78°C. It is only slightly soluble in water, freely soluble and miscible with chloroform, alcohol and other organic solvents such as petroleum, benzene, ether, fixed oils and essential oils. When shaken with milk it forms a good emulsion and this, especially skimmed milk, forms a good medium for its administration.

Impurities. Carbon tetrachloride often contains carbon bisulphide as an impurity, also traces of phosgene (carbonyl chloride) may occur. It is believed by some that these impurities, especially carbon bisulphide, greatly increase its toxicity. Strict standards of purity have, therefore, been recommended and a number of brands of the purified drug are on the market for medicinal use.

Pharmacological action. Carbon tetrachloride is a general protoplasmic poison. *Paramoecium caudatum* and free-living *amœbae* are instantly killed in 1 in 3,000 dilution; movements of chilomastix cease in 1 in 4,000 dilution.

When applied to the skin carbon tetrachloride is a local irritant, specially when its evaporation is prevented. On mucous membranes it produces preliminary irritation followed by anaesthesia. When given by the mouth, it has a burning taste; there is a feeling of warmth in the stomach due to mild irritation of the mucous membrane. Reflex stimulation produces increased peristaltic movements of the stomach and intestine, and 1 to 2 hours after a large dose a stool may be passed. The drug passes through the stomach unchanged. That a certain amount is absorbed is evident from the fact that such symptoms as dizziness and sleepiness appear soon after ingestion. Absorption occurs through the lymphatics, especially when fatty substances are present in the gut. By this route, the drug goes straight to the systemic circulation without passing through the liver and a sufficient amount

may be absorbed to cause respiratory and cardiac depression. Absorption may also take place by the portal route, and when this is the main channel of absorption, such symptoms as jaundice, vomiting, bilirubinuria usually occur, due to the toxic effects of the drug on the liver. Both clinical and experimental evidence is conclusive that if carbon tetrachloride is given with alcohol or fatty substances its toxicity is considerably enhanced. When given with olive oil, cream and absorbable fats, animals quickly show signs of intoxication. Patients feel drowsy and have a desire to go to bed. These observations show the importance of controlling the diet when the drug is given. Fats should be excluded from the diet. With non-absorbable fats such as castor oil or liquid paraffin, the absorption is not so much increased, but it is preferable to discard fatty substances altogether. Large doses do not appear to be proportionately more harmful than small ones; in other words, the drug appears to have a tendency to protect against itself. Even small amounts such as 0.1 c.cm. dissolved in alcohol and given intravenously have a marked toxic effect on the heart and respiration, whereas after oral administration and injection into the mesenteric veins, these effects are negligible on account of the detoxicating action of the liver. In patients with cirrhosis where the liver parenchyma is damaged, severe toxic effects on the heart and respiratory system have been recorded.

Liver. If an injection of a fairly big dose of carbon tetrachloride is given into the mesenteric vein of an animal, there is acute destruction of the liver cells, and jaundice develops. When absorbed from the gut, the drug is taken to the liver and produces fairly generalised fatty degeneration; with larger doses, necrosis develops, usually beginning in the centre of the lobule and spreading to the periphery. The liver function test (phenol-red test) may show great derangement of function. In severe cases the hepatic cells at the periphery of the acini show widespread infiltration with droplets of fat. In cats after such small doses as 0.25 c.cm. per kilo. the liver tissue is practically all destroyed. This liver damage reaches its maximum in 48 hours, after which rapid repair sets in, and in a few days little evidence of damage is left. In therapeutic doses in man some injury to the liver in the form of fatty infiltration probably always occurs, and perhaps some slight fatty degeneration and central necrosis. But where the liver is originally healthy and due precautions are taken to avoid excessive absorption, this is not sufficient to disturb the normal functions of the liver nor to cause any permanent injury. Any damage to the liver which may result is rapidly made good if the drug is not repeatedly administered. Continued and prolonged administration of carbon tetrachloride in dogs produces cirrhosis of the liver. There is no evidence to show that the drug has any damaging effect on the pancreas.

Carbon tetrachloride has a depressing action on the heart and respiration. It slows the beats of the heart, the contractions become weak and the blood pressure falls. The amount of bilirubin is increased and calcium is decreased in the blood. After severe injury to the liver, guanidin and guanidin-like substances in the blood are increased and there may be hypoglycæmia. Administration of calcium salts is beneficial in this condition. It has been shown that acute intoxication is more likely to occur when the dietary calcium intake is reduced. The blood in these cases shows decrease of calcium content and there are convulsive symptoms resembling tetany. The administration of calcium chloride intravenously or calcium and parathyroid extract orally produces a rapid cure in experimental animals. It has also been shown that after severe injury to the liver there is definite retention of guanidine in the blood, bilirubinæmia and hypoglycæmia. In dogs symptoms of nervous irritability, gastro-intestinal irritation and hypoglycæmia can be produced by giving guanidine hydrochloride. When calcium is given to these animals the symptoms abate. The administration of ammonium chloride and hydrochloric acid also counteracts the toxic effects of carbon tetrachloride by increasing the ionised calcium of the blood.

The action of carbon tetrachloride on the nervous system resembles that of chloroform. Slight giddiness and a feeling of relaxation and drowsiness are the only symptoms noticed after therapeutic doses.

Next to the liver, the kidneys are the organs most severely affected in experimental animals. In dogs large doses produce cloudy swelling of the convoluted tubules and fatty infiltration. In cats the effects are much more severe. It is probable that the drug only reaches the kidneys in sufficiently high concentration to injure them if the liver is damaged and cannot adequately deal with it. Carbon tetrachloride is well tolerated by pregnant women. The drug relaxes the isolated uterus.

Excretion. Some of the drug is excreted in the feces unchanged; some is absorbed and is excreted through the lungs, in fact, these organs are the main channels of excretion whatever may be the mode of administration. Only traces are found in the urine. According to Robbins (1929) the drug is not excreted by the kidneys.

Dosage and method of administration. The dosage and method of administration have varied greatly in different hands. Though doses ranging from 1.5 c.cm. to 10 c.cm. have been tried by eminent workers, 3 c.cm. may be considered to be a safe dose for an average adult. Chopra and McVail (1923) employed a 60 min. dose of the chemically pure drug with excellent results and with no untoward effects. A single dose of 3 to 4 c.cm. is safer than a smaller quantity given in

divided doses, since by the latter method more of the drug is absorbed into the circulation. The anæsthetic protective action of the drug itself on the mucous membrane of the intestine is probably an important factor in limiting absorption.

The drug has been administered in various ways. Hall recommended that it should be administered in hard gelatine capsules. The capsule is usually of 1.0 c.cm. capacity and care should be taken before it is put in the mouth that it is covered tightly. It should be swallowed promptly to avoid the chance of inhaling the drug into the larynx and trachea, which may produce collapse or inhalation pneumonia. A simple method is to administer the drug in water with or without a subsequent dose of magnesium sulphate. The drug is poured in a tablespoon or a small glass and covered with water. As it is insoluble in water and very heavy it remains at the bottom and the patient gets water first, then the drug and then more water. Magnesium sulphate has also been used as a vehicle with success. The action of the drug is not impaired by simultaneous administration of salts though it is said by some to increase its irritant action on the intestinal mucosa. The saline purgative can be given either with the drug or one to two hours later. Simultaneous administration of a saline purgative does not reduce the anthelmintic activity of the drug as is believed to be the case with chenopodium. Chopra and McVail used skimmed milk as a vehicle. The drug forms a good emulsion with it, the disagreeable taste is to a large extent concealed and the toxicity is not increased. Given by this method carbon tetrachloride produces a high percentage of cures with one treatment, probably on account of more thorough distribution of the emulsified drug in the intestines.

There is no necessity for preliminary fasting with this drug. The patient takes his usual evening meal and takes carbon tetrachloride the next morning, no food being taken for three hours after. Administration of the drug, immediately before or after food is not advisable. No fat or alcohol should be allowed a few days before or after the treatment.

Anthelmintic effects. There is no doubt that carbon tetrachloride is the most effective drug known for the expulsion of

hookworms of the genus *Necator*. In doses of 3 to 4 c.cm. one treatment removes 95 to 98 per cent. of the worms and completely cures 60 to 70 per cent. of cases of pure necator infections. It is much less effective against ankylostomes and ordinarily does not completely cure more than 30 to 40 per cent. of cases though probably 80 to 85 per cent. of the parasites are expelled. The drug has little effect on ascaris. On oxyuris, carbon tetrachloride has a very decided action and large numbers of parasites are removed by a single dose of 3 to 4 c.cm. by the mouth. Its effectiveness cannot, however, be accurately measured as re-infections very commonly occur. Oxyuris infections can also be treated by enemata of 6 oz. of warm skimmed milk to which 6.0 c.cm. of carbon tetrachloride are added. The patient is generally given a strong dose of salts the previous night to empty the lower bowel and before the enema is given the foot end of the bed is raised and the patient lies on the left side. The parasites expelled are all dead. Trichuris and strongyloides are not affected. Tænia and hymenolepis are not destroyed in the dog but in man the drug is of great value in removing both *T. solium* and *T. saginata*. Maplestone and Mukherjee (1931) obtained a cure rate of 84.6 per cent. in a series of thirteen cases. The patients, on the day of admission, had a meal of milk and bread only and first thing the next morning they were given a dose of carbon tetrachloride, shaken up in a saline purge (saturated magnesium sulphate solution). Carbon tetrachloride would, therefore, appear to be a better drug than male fern for the removal of the tapeworms, though male fern has held the field for such a long time. Carbon tetrachloride is also effective in the treatment of fasciolopsiasis and has been used in combination with tartar emetic in the treatment of schistosomiasis.

Advantages of carbon tetrachloride over other anthelmintics are :—

- (a) A high degree of efficacy against hookworms.
- (b) No preliminary dietetic treatment is necessary except that fats and alcohol should be avoided a few days before and a day or two after the treatment.

(c) The patient need not remain in bed and thus need not be away from his usual work.

(d) The entire treatment can be given at one time.

(e) The cost is nominal, a dose of carbon tetrachloride costing only a few pice.

The last three points are specially important when dealing with large labour forces

Toxic effects. The only symptoms complained of in human beings after therapeutic doses of carbon tetrachloride are a sensation of warmth in the stomach, slight nausea, giddiness, confusion of thought and a feeling of mild alcoholic intoxication an hour or two after its administration. The patient has a taste of boiled cabbage in the mouth after eructations. Vertigo, cephalalgia and somnolence of a transitory nature may occur. A feeling of relaxation and drowsiness follows, and the patient may fall asleep. Rarely, there is an uncomfortable feeling in the epigastrium, followed by diarrhoea. When excessive absorption occurs or larger doses are given there is stupor, dilatation of the pupils and irregularity of pulse; jaundice may be produced and rarely pain in the lumbar region, hæmaturia and albuminuria. Death may occur from collapse and extensive lesions in the liver and the kidneys have been seen. Sometimes deaths have occurred with small doses such as 45 minims (3.0 c.cm.). In a million and a half cases treated in Fiji, there was one death in 50,000. All deaths occurred in alcoholics or persons heavily infested with ascaris, where mechanical obstruction leads to increased absorption. This danger can be overcome by prescribing the drug with chenopodium. The habitual use of alcohol and a damaged liver increase the susceptibility to toxic effects.

If symptoms of poisoning occur a brisk purgative should be administered. If liver damage has occurred only symptomatic treatment is indicated. If muscular irritability is present calcium might be useful in view of the fact that there is marked calcium deficiency in the blood following bilirubinæmia.

There is a good deal of controversy regarding the toxic effects produced by carbon tetrachloride. Some workers pronounce it as being very poisonous and are of opinion that

it should not be used under any condition. Others consider it to be a harmless drug. Clayton Lane (1930) cited fatalities with such doses as 1.5 c.cm. and considers that it is a retrogressive measure to use carbon tetrachloride in preference to thymol. He does not consider the drug safe for mass treatment. The author's experience is that if the cases are selected properly and necessary precautions are taken, carbon tetrachloride is a safe drug. Thymol is not only more expensive but is liable to produce toxic symptoms more frequently. Deaths have also been recorded after thymol administration for helminthiasis.

Precautions and contra-indications. The drug should be pure and the dose should not exceed 5.0 c.cm. The whole dose should be given at one time and not divided. It should always be accompanied or followed by a saline purgative. The drug is contra-indicated in badly nourished and weak individuals and those having a low calcium content in the blood. If anæmia is present give iron and arsenic or a course of liver extract. Under no circumstances should it be given when cirrhosis or other organic disease of the liver co-exists or when there is advanced kidney disease. A diet rich in carbohydrates, proteins and calcium is beneficial. It is better to administer the drug three hours after a moderate meal. Some recommend milk or calcium lactate for several days before taking carbon tetrachloride. Preliminary starvation is dangerous. A treatment with carbon tetrachloride should not be given for several days after chloroform anæsthesia and it should be given to alcoholic subjects with caution. Idiosyncrasy to carbon tetrachloride may exist and small doses may produce very marked toxic symptoms.

Carbon tetrachloride can be given to malaria and kala-azar patients, preferably during the afebrile period. It is well tolerated by pregnant women and children. When heavy ascaris infections are present, it should not be given alone but in combination with oil of chenopodium.

Carbon tetrachloride and chenopodium. A combination of carbon tetrachloride and oil of chenopodium is more effective than either of the drugs alone. The reason is not far to seek. Carbon

tetrachloride itself is effective against pure necator infections and chenopodium alone for ascaris infections, whereas ankylostoma infections are readily cured by a combination of the two with a relatively high proportion of chenopodium. The effects of the two drugs on the host are independent. One does not increase the toxicity of the other while their action is supplementary to each other as far as the parasites are concerned. Dilution of chenopodium with carbon tetrachloride lessens the discomfort of taking the former drug and reduces the cost of treatment. The dose of the two drugs is so reduced as to be below the toxic limit.

Different proportions of these two drugs have been combined by various workers. Smillie and Pessoa use 2 c.cm. of carbon tetrachloride with 1.0 c.cm. of oil of chenopodium or 0.5 c.cm. of ascaridol. Soper (1924) pointed out that the proportion of the two drugs should depend on the nature of the worms harboured. Chopra and Chandler (1929) recommend for predominantly ankylostoma infections, or where ascaris is abundant, 2 c.cm. of carbon tetrachloride and 20 min. of oil of chenopodium; when ankylostomes are less numerous than necators 3 c.cm. of carbon tetrachloride with 10 to 20 min. of chenopodium are preferable. A mixture of carbon tetrachloride and oil of chenopodium in proportion of 3 parts to one part is considered a safe and efficient anthelmintic against *T. saginata*. Daubney and Carman, in a series of thirty patients had a cure rate of 97 per cent. in what they described as light infections. Maplestone and Mukherjee, however, consider that carbon tetrachloride, by itself, given in a single dose, is as effective as the mixture.

Oil of chenopodium and carbon tetrachloride are readily miscible but the latter drug is more volatile and if the mixture is old the proportions will change. It is advisable to prepare it fresh. The disadvantage of this combination is that it is extremely obnoxious to take. Chenopodium can be given separately in a capsule, followed by carbon tetrachloride in water, salt or milk, either immediately or one or two hours after. When mass treatment is given the mixture is more convenient.

Preparations.

Carbon tetrachloride (U.S.P.X.) **Synonym.**—Tetrachlorethane. **Commercial name.**—Necatorine. **Dose** 60 min. (8.0 c.cm.) as anthelmintic for adults.

Children of one year should be given 10 min., for a child of 10 years 30 min., and a youth of 16 years 40 min. Milk is the best vehicle for administration. Capsules of carbon tetrachloride are available containing 20 min. in each (P. D. & Co.); capsules of 0.3 c.cm., 1 c.cm., and 3 c.cm. are also marketed.

OTHER CARBON DERIVATIVES

It has already been pointed out that compounds of chlorine with ethane, ethylene, and methane series show anthelmintic properties and even compounds of the propane and butane series have been tried. Ethylene dichloride or dichlor-ethylene, $C_2H_4Cl_2$ is inferior to C_2Cl_4 which is as effective as CCl_4 . Carbon trichloride or hexachlorethane, C_2Cl_6 , is entirely ineffective; chloroform $CHCl_3$ has only slight anthelmintic action. It would appear that high solubility is correlated with increased absorption and consequent lowered anthelmintic action and increased toxicity. Very low solubility has the opposite effect and as the solubility becomes less and less the anthelmintic activity decreases. From our experience with these compounds it appears that solubility of something like that of carbon tetrachloride (1 in 1,250 of water) is the best from an anthelmintic point of view.

Chloroform. Chloroform is a well-known general anæsthetic, but it has been used very rarely internally except in small doses. The dose in the British Pharmacopœia is 1 to 5 minims, but as an anthelmintic as much as $\frac{1}{2}$ to 1 drachm (2 to 4 c.cm.) has been given. When administered in small doses and in a diluted form, its irritant action on the gastro-intestinal tract is not marked, the carminative and sedative action being more prominent.

Anthelmintic effects. As an anthelmintic, chloroform has been used either alone or in combination with other substances. It was used against tapeworm infections as early as 1897. Schultz (1911) tried it in hookworm infections of dogs with good results and suggested a mixture of chloroform and castor oil for use in man, but it did not prove to be very effective though many worms were expelled. The results on ascaris and whipworms were also not very striking. Chloroform in combination with oil of chenopodium is more potent than chloroform alone and has been shown by Caius and

Mhaskar (1923) to expel a high percentage of both ascaris and hookworms. A vigorous after-purgative is always necessary after its administration as most of the worms do not die but get benumbed and hence should not be allowed to recover from the stupefying effects of the drug. Chloroform used for internal administration must be of the purest quality, freed from all the common impurities such as hydrocarbons, chlorides, chlorine, free acids, phosgene, etc. The drug is no longer used as an anthelmintic since the introduction of more effective and comparatively less toxic carbon tetrachloride.

Toxic symptoms. These resemble the symptoms seen after carbon tetrachloride. Even 30 to 45 min. produce unpleasant symptoms and as the dose is increased beyond 45 min. the toxic effects become more marked. Dogs, after two doses of 3 c.cm. each, refuse food, vomit, are seized with mania-like symptoms, and die. Extensive changes in the liver are noticed in these animals, the lobules becoming yellow in colour and there is marked degeneration of the parenchyma, which shows mottling and there are hæmorrhages in lungs, stomach, intestines and diaphragm. In man the symptoms produced are those of gastro-intestinal irritation, but after absorption of large doses, drowsiness, loss of consciousness, coma, and death may occur. Fatty degeneration and central necrosis of the lobules of the liver occur, as in the case of carbon tetrachloride. Collapse and death may occur from severe gastro-intestinal irritation.

Eucalyptus oil and chloroform mixture. A mixture of eucalyptus oil and chloroform was introduced under the name of Manson's mixture. It contains eucalyptus 2 gm., chloroform 2 gm., and castor oil 40 gm. Most of the authorities who have tried this mixture agree that it is dangerous and not efficacious. Exclusion of eucalyptus from the mixture does not lower its anthelmintic efficacy showing that the main action is due to chloroform.

TETRACHLORETHYLENE

It is also known as perchlorethylene or carbon dichloride. It is an unsaturated chlorinated aliphatic hydrocarbon, having the formula, C_2Cl_2 . It is a heavy liquid, having a specific gravity of 1.6, boiling point varying between 110° — $120^{\circ}C$ and chlorine content of 85.5 per cent. It is very insoluble in water (1 in 10,000 or less). The drug is fairly stable in all climatic conditions, but it should be kept away from the air in well-stoppered amber bottles.

Pharmacological action. It is non-irritating and does not produce any local effect on the mucous membrane. Absorption of the drug,

when given by the mouth varies in different animals. Mice and rabbits show signs of narcosis when given in doses of 4 c.cm. per kilogram of body weight. Cats and puppies behave similarly but the effects are not so marked. Dogs can tolerate an enormous dose (10 c.cm. per kilo. body weight) without showing any signs of intoxication. Lamson and his co-workers (1929) in studying the absorption of the drug in dogs, puppies and cats stated that after injecting doses up to 10 c.cm. per kilo. into a loop of intestine, no tetrachlorethylene could be recovered from the expired air. Puppies however gave definite evidence of absorption; 4 c.cm. per kilo. raised the concentration of the drug to 3 to 6.3 mgm. per litre in the expired air in one and 3.2 to 4.7 mgm. in the other. Cats showed practically the same degree of absorption. Fatty substances or alcohol increase the absorption of the drug.

Blood pressure. When dogs are anaesthetised with excessive amounts of tetrachlorethylene or when it is given intravenously, it produces a marked fall in blood pressure and temporary cessation of respiration. If the same dose is given into the portal vein instead of the femoral, there is no fall in blood pressure, possibly because the liver fixes this substance. In man the dose of tetrachlorethylene being comparatively very small, *i.e.*, 2 to 3 c.cm., the effect on blood pressure is practically negligible.

Toxicity. Toxicity varies in different animals. Doses of 5 c.cm. per kilo. body weight kill rabbits in 10–20 hours. Mice can stand doses of 4–5 c.cm. per kilo. for nearly 10 hours before death ensues. In cats, doses varying from 5–10 c.cm. become fatal in 6–36 hours. In dogs, death occurs with doses varying from 10–25 c.cm. and doses below that are generally well retained without the appearance of any toxic manifestations. The pathological changes produced in the tissues especially of the liver and kidneys which are well-marked in chloroform or carbon tetrachloride poisoning, are very slight. This will depend on the rate of absorption from the intestine. Dogs do not exhibit any signs of liver necrosis or any change in the glomeruli or tubules of the kidney. The livers of cats and puppies may show a certain amount of fatty degeneration, depending on the amount of absorption of the drug.

As an anthelmintic. Hall and Shillinger (1925) were the first to investigate the anthelmintic properties of this drug. Judging from the promising results of experiments with a series of halogenated hydrocarbons in experimental animals, they considered tetrachlorethylene would be as effective as carbon tetrachloride in the treatment of hookworm disease, with the additional advantage of its lower toxicity. The efficacy of tetrachlorethylene as an anthelmintic, as in cases of other related compounds, depends upon the chlorine content. The efficacy is said to be increased with the amount of available chlorine. From this point of view, and also because of its being very

sparingly soluble in water the chances of absorption from the intestine are decreased. It has therefore been used in the treatment of human ankylostomiasis. The drug was found to be ineffective in human ascariasis. For trichuris infection tetrachlorethylene is considered to be superior to oil of chenopodium. Brosius, Peon and Carroll (1927) treated 24 cases of hookworm infection with tetrachlorethylene and obtained a cure rate of 91.7 per cent. They, however, observed toxic symptoms such as dizziness, epigastric pain, nausea, and vomiting in all but three cases. A combined treatment, 1.8 c.cm. tetrachlorethylene and 0.6 c.cm. oil of chenopodium, removed 94 per cent. necators and 48 per cent. ankylostomes.

Maplestone and Mukherjee (1933) concluded that tetrachlorethylene, used after the method described hereafter, is at least as efficient as tetrachloride, and it is safer than the latter on account of its not damaging the liver and kidneys when given in therapeutic doses. Another great advantage, especially when dealing with a large labour force, is the fact that alcohol does not increase its toxicity. The cure rate with tetrachlorethylene is probably slightly greater than with tetrachloride, as the dose given is larger (4 c. cm.) than the latter. This may explain the difference, but even if this is the explanation of the higher number of cures with tetrachlorethylene the practical advantage of it still remains, because if it can be safely given in larger doses than tetrachloride and cures more persons, it is a better drug for the purpose of treating hookworm infection.

Method of administration and dosage. No very special preparation is necessary before the treatment is started. The patient should be advised to take a light diet the evening prior to treatment and no breakfast is allowed on the day of treatment. The drug is given shaken up in two ounces of magnesium sulphate solution and the full dose for an adult is 3 to 4 c.cm. When combined with oil of chenopodium, the ratio should be 3 to 1, i.e., with 3 c.cm. of tetrachlorethylene 1 c.cm. of oil of chenopodium. Patients under sixteen years of age should receive a reduced dose.

The actual details of treatment as recommended by Maplestone and Mukherjee are as follows :—

Two ounces of saturated magnesium sulphate solution are placed in a flask or bottle of three or four ounces capacity and four c.cm. of

tetrachlorethylene and one c.cm. of oil of chenopodium are added to it. The flask is corked and shaken until the drugs are distributed throughout the mixture in the finest possible droplets; the dose is then given to the patient immediately, before the drugs have time to coalesce into larger drops and float to the surface, as will happen if the mixture is left standing. This method of shaking was adopted in the first place because it was stated that it was dangerous to give tetrachloride unless it was in finely divided droplets, and the same method has been continued with tetrachlorethylene because it is considered that the even diffusion of the drug throughout the draught gives it a much better chance of coming into contact with all the worms on the gut wall and is, therefore, more efficient than if given as an undivided globule of one drachm.

Toxic symptoms. Lamson and his co-workers (1929) fully investigated the relative toxicity of carbon tetrachloride and tetrachlorethylene on experimental animals and advocated the use of the latter in human ankylostomiasis because of its comparative safety. There has so far been no report of deaths with this drug and this is correlated with its low rate of absorption. Clinical observations, however, point to the fact that the drug is absorbed to some extent from human intestine, but not in amounts sufficient to produce damage of the kidney or liver cells. Kendrick (1929) reported only one case of grave intoxication in a total of 1,500 treatments; in this case there were signs of giddiness which developed into unconsciousness with twitchings of the whole body. Maplesone and Mukherjee (1929) observed varying symptoms of giddiness, vomiting or drowsiness in 8 out of 38 cases treated with tetrachlorethylene alone, and in 26 out of 37 cases treated with a combination of tetrachlorethylene and oil of chenopodium.

At present, from the results of clinical observations, it seems that tetrachlorethylene would be a very safe drug to employ as an anthelmintic and the danger of toxic symptoms can be avoided if alcohol and fatty substances are withheld during treatment.

Iodoform. Iodoform has occasionally been used for removing ascaris in man, in doses of 0.01 to 0.06 gm. three times a day in combination with sodium carbonate. Hall and Foster found this drug useless as an anthelmintic in dogs in much larger doses than those used in man.

CHAPTER IV
ANTHELMINTICS ACTING ON NEMATODES (Contd.)
THE ESSENTIAL OIL GROUP
OIL OF CHENOPodium

Synonyms: American worm seed, Mexican tea.

Chenopodium has been used as a household remedy against intestinal parasites for a long time. It was used by American Indians in the days of Columbus. The oil was originally used many years ago against ascaris, but was not popular because of the toxic and sometimes fatal effects produced in many cases. Schüffner and Verwoort (1913) tried it against hookworm in Sumatra in doses of 3 c.cm. in combination with castor oil and chloroform with excellent results. From that time the drug came rapidly into use. It came to the forefront during the Great War when the supply of anthelmintic drugs such as santonin and thymol was curtailed.

The active oil is obtained from *Chenopodium ambrosioides* var. *anthelminticum*, or the *American wormseed* belonging to the N. O. Chenopodiaceæ or the goosefoot family. A number of other species also yield the essential oil and *Herba chenopodia* is official in the Austrian Pharmacopœia. In India at least seven species of chenopodium grow, but only two of them yield oil having anthelmintic properties, these being *C. ambrosioides* and *C. botrys*. A variety of *C. ambrosioides* is cultivated in Java.

Chemical composition and properties. Chenopodium contains 40 to 80 per cent. of *ascaridole* which is chemically allied to essential oils; this is the anthelmintic as well as the toxic constituent. The oil has no definite boiling point and when it is heated to 100°C. in the air it explodes with violence. Different specimens differ much in their physical characters, the colour may vary from pale yellow to light golden yellow. The toxicity of different stocks also varies greatly and the samples met with in the market are often adulterated up to the extent of 50 per cent. The whole oil as well as ascaridole are practically insoluble in water and are very slightly absorbed; on this quality its anthelmintic action is chiefly dependent. Ascaridole is

altered by heat into a less volatile substance which has much weaker anthelmintic properties. Distillation should therefore be carried out with great care.

Besides the volatile substances chenopodium also contains certain terpenes—limonene, cymene and terpinene. Specimens of chenopodium oil met with in commerce vary a great deal in activity on account of variations in their ascaridole content. The drug now on the market is properly standardised.

Pharmacological action. Oil of chenopodium like other volatile oils is diffusible and irritant to the skin and mucous membrane. It has germicidal properties. It kills protozoa and was at one time recommended in amœbic dysentery. Internally the oil has a sharp burning taste, produces salivation and reflexly stimulates the flow of gastric juice. The peristaltic movements of the intestines are decreased and a constipating effect is usually produced. Large doses produce severe irritation of the whole of the gastro intestinal tract. The oil is absorbed from the stomach with difficulty, but absorption may take place from the intestines.

The oil has a markedly depressant action on the circulation, the blood pressure shows a considerable fall in experimental animals after intravenous injections of 0.02 c.cm. per kilo. The pulse becomes slow and weak; there is also marked depression of respiration.

The oil has a well marked effect on the central nervous system. There is at first a transitory stimulation followed by a marked depression of the respiratory, cardio-vascular and other centres in the medulla. Later, the higher centres are affected, giving rise to stupor and coma. The special senses, especially sight, may be affected. Cases of blindness and deafness have been reported after use of chenopodium oil.

Whether given by the mouth or intravenously the oil is partly excreted by the lungs and partly by the kidneys. The elimination is slow and neither the oil nor the products of its decomposition can be readily detected. Small doses have a diuretic effect by mildly irritating the kidneys; large doses may set up inflammation and albuminuria. Subcutaneous injections of the oil in animals set up renal irritation.

In vitro experiments show that the action of the oil is probably due to penetration through the cuticle and into the cells of the parasites, resulting first in stimulation and then paralysis of the musculature. In such dilutions as 1 in 10,000 to 1 in 5,000 there is at first tonic contraction of the muscles of ascaris, followed by relaxation and paralysis, so that the parasites cannot resist the intestinal peristalsis. Experiments on earthworms show that the toxic effect is much greater at 37°C than at 21°C.

Anthelmintic effect. Oil of chenopodium has a marked action on all kinds of intestinal nematodes, but little or no action on large tapeworms. It is particularly effective against ascaris

and is as good an ascaricide as santoin, a very high percentage of worms being removed even if a complete cure is not effected. The drug does not kill the parasites but only paralyzes them, and they must be expelled by free purgation. Against hookworm infection chenopodium is a particularly useful drug. It is less effective against necators than carbon tetrachloride, but is about equally effective against ankylostomes. In doses of 30 min. it can be depended upon to remove about 90 to 95 per cent. of necators and about 80 to 85 per cent. of ankylostomes.

The oil is not so effective against trichuris because of the situation of these worms in the colon and cæcum. Large numbers of threadworms are expelled but here also the effectiveness is less than on the worms situated higher up in the gut. Carbon tetrachloride is probably more effective against these worms. Its anthelmintic efficacy against clonorchis, hymenolepis and strongyloides is doubtful. Intramuscular injections of chenopodium or ascaridole are said to be useful in filariasis, the initial dose being 0.5 c.cm. gradually increased to 2.0 c.cm. Injections are said to cause disappearance of filaria in many cases.

Dosage and method of administration. The maximum dose of the oil is 3 c.cm. given in three doses of 1 c.cm. each, at intervals of an hour. The last dose is followed one hour later by an ounce of saturated solution of magnesium sulphate. This dosage cannot be adopted in general treatment, because it frequently gives rise to severe toxæmia especially in ill-nourished patients.

Most of the authorities recommend 1.5 to 2.0 c.cm. (30 min.), divided into two or three doses, given at intervals of one hour. This method is both safe and efficient. Doses recommended for children are, 3 capsules of 2 min. each for a child of 3, 3 min. each for a child of 5, 5 min. each for a child of 10 and 7 min. each for a child of over 12 years. Weak individuals should have reduced doses, according to their state of health.

The drug may be given in the morning in doses of 10 to 15 min. at 7, 8 and 9 a.m. Some authorities allow an interval of 2 to 3 hours between the doses and some prefer to give the anthelmintic and purgative together, 10 to 20 drops being given

with senna or mixed with castor oil. To conceal the taste it may be mixed with olive oil or almond oil.

Pure ascaridole is now on the market and is used in doses of 1.0 c.cm. for an adult given in 2 or 3 divided doses an hour apart. Pessoa (1923) gave 1.0 c.cm. in one dose in hard gelatine capsules on an empty stomach, followed by a saline purgative half an hour later; a preliminary purgative is not necessary. For children up to 5 years, 1 to 2 drops of ascaridole in an emulsion of 10 to 20 c.cm. of castor oil is the best. For children between 6 and 15 years, one drop for each year of age in gelatine capsules followed an hour later by a saline purgative is generally recommended.

Chenopodium has a very obnoxious and nauseating taste and is preferably given in hard gelatine capsules, although it can be taken in syrup or in a lump of sugar. The results, obtained when given in the form of emulsion, are inferior to those when the oil is given by itself. It has also been shown that the drug is less toxic and its anthelmintic effects are not only as good but better if no preliminary dietary measures are adopted and no pre-purgative is given. This makes the oil a useful drug for labour forces in the field. It is preferable to give the oil three hours after a moderately light morning meal.

Necessity of a purgative. A post-purgative should always be administered after chenopodium. It has been pointed out that chenopodium inhibits intestinal peristalsis and thereby tends to produce constipation. The administration of castor oil immediately after it retards the absorption of the drug and helps its elimination from the alimentary canal. Certain fixed oils such as olive oil prevent the toxic effects of chenopodium. If a saline purgative is to be used it should be given at least 2 hours after administration of the oil as it has been shown that simultaneous administration of salts greatly reduces the anthelmintic efficacy of the drug.

Chenopodium has been tried intramuscularly and is said to have an anthelmintic effect when given in this way. The mixture prescribed for this purpose consists of chenopodium oil 60 c.cm., camphorated oil 60 c.cm. and resorcin 4 gm. The usual dose is 4 c.cm. of the mixture injected into the buttock. Its vermifugal action against hookworm is

small but is quite efficacious against trichuris. Intravenous injections of the oil in doses of 2.0 c.cm. have been given, with the idea that after absorption into the blood the oil will reach the hookworms, which have anchored themselves to the mucous membrane and which will then let go their hold. Given in this way the oil may produce a mild collapse.

Toxic effects. The oil of chenopodium is a toxic substance and causes severe irritation of the mucous membranes. Rabbits die of vomiting, convulsions, coma and paralysis after 0.5 c.cm. doses; 0.25 c.cm. per kilo. is fatal in cats. Fish die in dilution of 1 in 8,000 in water and are narcotised in 1 in 25,000. A full dose in an animal if repeated within a few days may cause death, and sensitiveness to the oil persists for at least 5 to 9 days. This should be remembered when treating unsuccessful cases in man. In man it sets up severe gastro-intestinal irritation; such a dose as 3 c.cm. produces nausea, vomiting, severe abdominal pain and finally paralysis of the gut. A certain amount of dizziness is nearly always present and there may be slight deafness and ringing in the ears. After excessive doses extreme dizziness, a feeling of intoxication, prostration, headache, drowsiness and unconsciousness occur, showing that there is severe toxæmia. The face is flushed, respiration slow, pupillary reaction sluggish and convulsions may follow giving place to flaccid paralysis. Albuminuria is present in severe cases and there may be hæmaturia. Autopsy shows severe inflammation of the gastro-intestinal tract, liver, and kidneys, and hyperæmia of the brain; there are fatty changes in the parenchyma of the liver and the kidneys. Deafness may sometimes persist. Children are more susceptible to the effects of the oil than adults and it is advisable not to exceed the prescribed dosage. It is better to use some other anthelmintic in children under 5 or 6 years of age and in very old and debilitated individuals. Owing to its slowness of absorption the toxic symptoms may appear a day or so after administration, and cumulative effects may be produced by smaller doses several days apart. In man death has been reported from ingestion of half an ounce or even less. Tolerance is decreased by starvation and debility, and increased by fixed oils.

Treatment of poisoning. As soon as inordinate sleepiness and depression or any other symptoms of intoxication appear, the administration of the drug, if all the capsules have not been given, should be stopped and a brisk purgative given. The stomach should be quickly washed out. There is no antidote known and the treatment is, therefore, entirely symptomatic. Respiratory and cardiac stimulants should be given.

Precautions and contra-indications. *Chenopodium* oil should be given with caution and in small doses when disorders of the heart and kidneys are present. It is forbidden in chronic nephritis and organic disease of the heart, and where hepatic and gastro-intestinal disorders are present. Prior to the administration of *chenopodium* against hookworm it is better to administer iron and arsenic and liver extract, especially when the patients are anæmic.

Preparations.

Oleum chenopodii (U.S.P.X.). It is distilled with steam from the fresh above-ground parts of the flowering and fruiting plant of *Chenopodium ambrosioides*. Dose 10—30 min. (1 to 2 c.cm.); for children as many minims as the number of years up to 10 years.

Ascaridole (N. O.). Dose 10 c.cm. A synthetic ascaridole has been prepared which in doses of 4 drops for each year of age of children and 70 drops for an adult is an effective anthelmintic.

OTHER ESSENTIAL OILS USED AS ANTHELMINTICS

A number of essential oils have been used in the treatment of intestinal worms but none of them have any specific action against any of the parasites.

Oleum eucalypti. The oil is distilled from the leaves of *E. globulus*, *E. dumosa* and a number of other species. The chief constituents of the oil are pinene, eucalyptol (cineol) and aldehydes of fatty acids. It has been used as an anthelmintic in combination with chloroform but its action appears to be very mild. Caius and Mhaskar (1920) gave it in 40 min. doses in the form of a mixture with gum acacia and castor oil. Doses of 60 min. and over produced giddiness, and vomiting, probably owing to the presence of aldehydes. It was quite ineffective against hookworms and had little or no effect against ascaris and whipworms. Pure eucalyptol has also been tried; it is much less toxic but the vermifugal action against intestinal parasites is feeble.

Oleum cajuputi. Cajuput oil is a volatile oil distilled from the fresh leaves and twigs of *Melaleuca leucadendron*, var. *minor*, *M. viridiflora*. It is a green-coloured oil with an aromatic odour and a pungent taste. The chief constituents are: cajuputol, which is the same as eucalyptol or cineol, terpineol, small amounts of pinene and traces of aldehydes. The oil has, therefore, the same active principles and same action as oil of eucalyptus.

It has been used as an anthelmintic in the gold mines of Guiana in the treatment of mild hookworm infections. Caius and Mhaskar (1920) tried the oil and found that even in 60 min. doses (the maximum tolerated dose) hookworms were very feebly affected and ascaris and whipworms were not attacked at all. The oil of cajuput cannot, therefore, be recommended as an anthelmintic.

Oleum terebinthinae. Common turpentine is an oleoresin obtained from several varieties of pines, chiefly from *Pinus palustris*. There are several varieties of turpentine oil on the market but the rectified oil is the only variety used for pharmaceutical purposes. Pure oil is a colourless liquid chiefly composed of one or more terpenes. Its anthelmintic dose is $\frac{1}{2}$ to 4 drachms, usually combined with castor oil. **Hausius terebenti** is sometimes prescribed; it consists of the oil combined with a drachm of glycerine and an ounce of cinnamon water.

Oil of turpentine is irritant to the skin and mucous membrane. It is readily absorbed from the alimentary canal and circulates in the blood unchanged. It is excreted through the skin and lungs but mainly through the kidneys, partly unchanged and partly as terpenols in combination with glycuronic acid.

Oil of turpentine is a toxic drug and half an ounce has proved fatal in children. In larger doses in adults severe gastro-intestinal irritation is set up, followed later by acute nephritis and painful micturition. The medullary centres are stimulated, producing at first excitement, delirium, and convulsions and later paralysis. Pain in the chest due to bronchitis is set up by irritation of the respiratory passages. If symptoms of poisoning occur the gut should be evacuated by large doses of magnesium sulphate; stimulants such as coffee should be administered.

As an anthelmintic, the oil of turpentine in doses of $\frac{1}{2}$ to 1 ounce has been successfully used in man. Some authorities have discouraged its use on the ground that it is likely to produce nephritis during excretion. In large doses, as used for expelling worms, it acts as a purgative and is not absorbed in sufficient quantities to cause renal irritation. Tapeworm infestations have been treated with one ounce doses in combination with castor oil with satisfactory results. Caius and Mhaskar (1920) treated a series of cases of hookworm with oil of turpentine, but the results were disappointing. All the evidence is, therefore, against its use as an anthelmintic except possibly for tape-

worms. Saline or soap enemata containing an ounce of turpentine are effective in expelling oxyuris.

Oleum tanceti (Tansy.) This oil is distilled from the flowering tops and leaves of tansy, *Tanacetum vulgare* belonging to N. O. Compositæ. It is a yellowish brown liquid consisting of thujone, borneol, camphor and a number of resins. It has been tried as an anthelmintic but is found to be wholly ineffective against hookworm, ascaris and whipworms. It is also a toxic drug and even in therapeutic doses produces vomiting and giddiness. The leaves and tops of *Tanacetum vulgare* have been used in the form of an infusion or as an enema to expel ascaris and oxyuris.

Oleum absinthii. The oil of absinth or vermouth or wormwood is obtained from the flowering tops and leaves of *Artemisia absinthium* belonging to N. O. Compositæ. It is usually a dark green oil consisting of a number of volatile principles and a bitter substance called *absinthin*. Medicinally absinth was chiefly used as a febrifuge and as an anthelmintic. It is a fairly toxic drug and is seldom used at present. The oil was tried by Caius and Mhaskar (1920) in the form of an emulsion against hookworms but the results obtained were not encouraging.

Oleum caryophylli. The oil of cloves is a thick yellow oil distilled from the flower buds of *Caryophyllus aromaticus*. The chief constituents of this oil are an unsaturated phenol called *eugenol* which forms 80 to 90 per cent. of the oil, acetyl derivative of eugenol (2 to 3 per cent.), caryophyllene, etc.

The oil has been tried against hookworms with little success. Cairns and Mhaskar (1922) by using an oil containing 92 per cent. eugenol in the form of an emulsion obtained satisfactory results. With 90 min. doses, administered in divided doses at half an hour intervals, 64.3 per cent. of hookworms were expelled, necators being much more vulnerable than ankylostomes. Oxyuris are also expelled in large numbers; ascaris and trichuris are not affected.

Pure eugenol and iso-eugenol have also been tried and found to have well marked vermifugal action against hookworms, their action resembling thymol. Both are well tolerated in doses of 1 to 1½ drachms, and with such dosage they produce a mild purgative effect, thus obviating the necessity for an after purgative.

Oleum betulæ. Betel oil is an essential oil obtained from the Indian betel vine commonly known as 'pan'. Leaves of this plant contain 30 to 70 per cent. of phenols consisting mainly of eugenol mixed with a small percentage of betel phenols. The oil in doses ranging from 30 to 90 min. has only a weak anthelmintic action against hookworms, expelling less than 20 per cent. of these parasites. The other intestinal parasites are not touched. The popular belief regarding the anthelmintic effect of betel chewing can be accounted for by the

elimination of immature hookworms from the body by constant spitting and so preventing them from migrating from the trachea into the oesophagus.

Oleum sassafras. The oil of sassafras is an essential oil distilled from the root of *Sassafras venifolium*. It contains 85 per cent. of safrol and has powerful antiseptic properties resembling those of clove oil. According to Carus and Mhaskar a dose of 30 to 60 min. expels 52.4 per cent. hookworms; other intestinal parasites are not affected. The oil resembles chenopodium oil in its action, but it is much less toxic to the host. Pure safrol has also been used in 60 min. doses and has been found a fairly good anthelmintic against hookworms.

Oleum anisi. This is obtained from distillation of ripe fruit of *Pimpinella anisum*. The oil is mainly composed of anethol but also contains small quantities of terpene. Its action closely resembles that of thymol. It is a fairly good vermicide, the maximum dose of 60 min. expelling about 50 per cent. of hookworms.

Pure anethol has also been used and is quite effective against hookworms expelling as many as 70 per cent. of the parasites. No toxic symptoms are met with either with the oil or with the active constituent anethol, even in one drachm doses.

Oleum cinnamomi. The oil is derived from *C. zeylanicum* and it contains large quantities of cinnamic aldehyde (50 per cent.) and is a powerful germicide. The oil has been tried but with disappointing results against ascaris, trichuris or hookworms.

Oleum rutæ. The oil is derived from the fresh leaves of common Rue, *Ruta graveolens*. It was used as an anthelmintic in India and is still used in some parts, the juice of the plant being given to children to expel intestinal parasites. Its anthelmintic efficacy is, however, slight.

Oleum copalba. It is quite useless as an anthelmintic even in doses of 30 to 60 min. against ankylostomes, necators, ascaris and trichuris.

CHAPTER V

ANTHELMINTICS ACTING ON NEMATODES (*Contd.*)

SANTONIN

Santonin is a classical remedy for the treatment of ascaris and oxyuris infections. It is obtained from *Artemisia maritima*, a plant whose flowering tops were used by the ancient Greek and Roman physicians as a remedy to expel intestinal parasites. Santonin is one of the most expensive drugs. Before the War practically the whole of santonin supply of the world came from Russian *Artemisia cina*. A number of allied species such as *A. maritima*, var. *stechmanniana* and *A. pauciflora* (*A. anthelmintica*) also grow in Turkestan. Owing to political and economic disturbances in Russia some years ago there was great scarcity of santonin, and *A. cina* having good santonin content was successfully cultivated in Holland. *A. maritima* or *A. brevifolia* grows abundantly in a state of nature in the dry inner valleys of the western Himalayas from Kumaon to Kashmir at an altitude of 4,000 to 12,000 feet above the sea level, and recently santonin has been obtained on a commercial scale from this source. Large quantities of artemisia with high santonin content are found to grow wild in the Kurram valley in the North-Western Frontier not far from the railway line.

Chemical composition and properties. The active principles of *A. maritima* are :—(1) A neutral principle, santonin which is responsible for the anthelmintic properties, (2) a bitter principle, artemisin (oxy-santonin) which is not very active, (3) a volatile oil, and (4) santonic acid. The amount of santonin extracted from the Russian *Artemisia* is usually 1.2 to 1.4 per cent., but may be as high as 2.3 to 3.6 per cent. The yield from the artemesia growing in Kashmir does not exceed 1.0 to 1.5 per cent. and the yield from that of Kurram Valley is slightly less. Santonin is a crystalline anhydride or lactone of santonic acid; it occurs in colourless, shining, flattened, rhombic prisms or as white crystalline powder. It is stable in the air, but on exposure to light develops a yellow colour due to the formation of an isomeride of santonin called chromosantonin.

Pharmacological action. Externally santonin has very little action. Taken by the mouth, it is tasteless at first but develops a bitter taste after a short time. Santonin, unlike most other anthelmintics is not

a gastro-intestinal irritant. It is quickly absorbed from the empty stomach. In the small intestine, the drug is acted on by the alkali present, sodium santoninate being formed. The sodium salt is soluble and is absorbed, but its effect on the circulatory and respiratory systems is slight in therapeutic doses. With large doses the symptoms produced are chiefly due to involvement of the central nervous system which is first stimulated and then paralysed. The special senses are usually affected most, and anomalies of vision and colour perception are commonly produced. At first white objects appear bluish, this is soon followed by xanthopsia or yellow vision which may persist for a few days and then disappear; blue seems green and violet is scarcely perceived. The usual dose producing these symptoms is 0.2 gm., the effect being probably on the cranial nerves. Smell, taste and hearing are sometimes affected. When large quantities of santonin are absorbed, twitchings and epileptiform convulsions, resembling those occurring in strychnine poisoning, are produced. In man convulsions rarely occur, but they are common in the dog and the rabbit. The animal usually dies of asphyxia from stoppage of respiration. Santonin is chiefly eliminated in the urine partly unchanged and partly in the form of oxy-santonin which gives the urine and sometimes the faeces a deep yellow colour. This colouration resembles that produced by anthracene purgatives, such as rhubarb, whose active principles are excreted in the urine. The two can be differentiated by the fact that by shaking the urine with a little lime water or barium water the santonin colouration remains in solution while the anthracene bodies are precipitated. Elimination of santonin begins quickly, but may go on for several days.

In vitro, ascaris are not killed even by saturated solutions of santonin in olive oil or castor oil. The parasites, however, become irritated and try to escape from the proximity of the drug. The irritant effect of the drug causes the parasites to move about in their efforts to escape, thus driving them into the colon whence they are expelled by a purgative. This irritant action can also be seen on the muscle tissue of leeches and worms; it is specific and is probably due to the presence of the lactone group though some believe that the anthelmintic action is in no way correlated with the structure of the lactone. It is not produced by santonic acid and is not apparent on the muscles of the vertebrates. The presence of dilute bile and alkali appears to increase markedly the toxic action of santonin on the parasites.

Santonin as an anthelmintic. Santonin is considered the most effective drug against ascaris, with the possible exception of oil of chenopodium. It is useless in intestinal taeniasis. Santonin acts best when combined with 3 or 4 grains of calomel and followed by a saline purgative six hours later. Calomel stimulates the flow of bile which enhances the toxic action of

santonin on the parasites. Santonin is best prescribed in the form of a powder either as coarse crystals or as trochisci. In the form of coarse crystals as ordinarily sold it is preferable to the finely divided powder, as the latter is liable to produce toxic symptoms. Alkalies dissolve it forming soluble alkaline santoninates which are usually absorbed rapidly, and therefore this combination should be avoided.

In determining the dosage for children a good rule is to give $1/6$ grain for every year of age; for adults 1 to 5 grains according to the general constitution of the patient may be given. The preliminary preparation of the patient and after-purgative are most important considerations in santonin administration. The following procedure has been used successfully at the Calcutta School of Tropical Medicine:—

The patient is given his last meal at 5 p.m., no food being allowed after that. In severe infections it is advisable to keep the patient on light diet for 24 hours previous to administration of the drug. At 10 p.m. 3 grains (0.2 gm.) of santonin combined with 3 to 5 grains (0.2 to 0.3 gm.) of calomel are given. At 6 a.m. the following morning, $\frac{1}{2}$ to 1 ounce saturated solution of magnesium sulphate or sodium sulphate is given. The stool should be examined for 72 hours after treatment and should be re-examined about 10 days later; if negative the patient may be considered cured.

As a rule no symptoms are observed, but nausea followed by vomiting may be produced. By using the above method 18 out of 19 cases were cured in one series. Santonin is a poisonous drug and idiosyncrasy to the drug is common. It is, therefore, recommended to give $\frac{1}{3}$ or $\frac{1}{2}$ of the total dose the first time and if no sensitiveness is shown the drug may be repeated.

Some authorities give santonin combined with an equal or larger doses of calomel every morning for 2 or 3 days in succession and repeat the process every 3 or 4 days as long as eggs are found. This procedure is likely to lead to toxic effects. Some observers consider it inadvisable to use an oily purgative such as castor oil with santonin, as it is likely to increase absorption; others consider that it inhibits absorption.

Combination of santonin and chenopodium. Maplestone and Mukherjee (1931) reported very encouraging results by combining santonin with chenopodium in the treatment of roundworm infestations. The method employed by them consists in the administration of 5 grains (0.3 gm.) of santonin in powder form and 1 c.cm. of oil of chenopodium in a capsule at the same time. A saline purgative is given after two hours. According to these workers santonin cures 60 per cent. of adult and 48.2 per cent. of children and the figures for combined treatment (santonin and oil of chenopodium) are 92.3 per cent. and 54.8 per cent. respectively.

Santonin is a toxic drug and should on no account be prescribed unless the diagnosis is made by thorough examination of the stools. The practice of prescribing santonin on the mere assumption of parasitic infestation is to be deprecated.

Subcutaneous, intramuscular and intravenous injections of 'santonin-sodium' have been successfully tried against ascaris.

Other uses of santonin. Santonin in doses of 3 grains for three days has been used in the treatment of amœbic dysentery and sprue, the yellow santonin being specially recommended in the latter condition. It has also been used in long-standing cases of diabetes associated with nervous disturbances particularly numbness of the extremities and pain of the sciatic or brachial plexuses. Such pains are sometimes relieved by such minute doses as 1/60 grain (0.001 gm.) or less, three or four times a day. The urinary sugar may diminish and the nervous symptoms abate with doses of santonin gradually increased from 3 grains (0.2 gm.) to 10 grains (0.6 gm.) daily. Patients susceptible to the drug should be previously tested by giving $\frac{1}{2}$ grain (0.03 gm.) and it should not be continued for more than 10 days. Santonin also relieves the lightning pains of *tubes dorsalis* the initial dose for this purpose being 1/120 to 1/60 grain (0.5 to 1.0 mgm.). It has been used in the treatment of epilepsy in doses of 2 to 5 grains (0.12 to 0.3 gm.). In small doses of 1/60 to 1/6 grain (1 to 10 mgm.) it has been recommended in the treatment of retinitis, amblyopia, and colour-blindness on account of its stimulant action on the retinal nerves.

Toxic effects. Toxic manifestations are usually evident when the drug is rapidly absorbed and these, in their turn, depend on the conditions of the alimentary tract favouring or retarding absorption. Children are more susceptible and the fatal cases reported are entirely among infants. Adults as a

rule are not seriously affected by doses less than 7 or 8 grains (0.5 gm.). In infants under 3 years, death may occur with a one grain dose ; the drug should therefore be used very cautiously in them. Repeated use of the drug is known to lead to tolerance.

Symptoms of santonin poisoning vary from slight manifestations of anomalies of vision to convulsions, coma and death. In mild poisoning digestive and ocular disturbances alone are observed, but in severe cases disturbances of the central nervous system predominate. Headache, vertigo, mental confusion, hallucinations, weakness, profound prostration, somnolence passing on to unconsciousness may develop. The diarrhoea is often profuse and the stool may contain blood ; convulsions, coma and death may follow. The heart becomes slow and feeble and there may be syncope from the fall of blood pressure due to depression of the heart and dilatation of the blood vessels. The kidneys and urinary passages are irritated producing painful micturition, albuminuria and hæmaturia. Tremors, spasms of muscles, and loss of speech have also been noticed.

Treatment of poisoning. This consists in rapid and thorough emptying of the bowels by purgatives and an enema. A central emetic like apomorphine may be given. Stimulants such as atropine, caffeine, or camphor, may be administered, and the patient kept warm. If convulsions are present repeated doses of chloral hydrate or inhalations of chloroform or ether may be tried. If respiration fails, artificial respiration should be resorted to.

Precautions and contra-indications. It is advisable not to give santonin on an empty stomach as it is soluble in the gastric juice and may be absorbed. It is preferable not to give it with an oily cathartic. Fever is not a contra-indication to the administration of this drug.

Preparations.

Santonica with a santonin content of 1.5 to 3 per cent. is used in $\frac{1}{2}$ to 1 drachm (2 to 4 gm.) doses as an anthelmintic.

A combination of santonin and bile called **santonin bile** has been prepared but it may produce toxic symptoms from rapid absorption

Santoninum. Dose 1 to 3 grains; U.S.P. dose 1 grain (0.06 gm.); in the French Codex $1\frac{1}{2}$ grains as a single dose, the maximum dose given during 24 hours being 5 grains. **Chromosantonin** (N.O.) or golden santonin is a modification of ordinary santonin formed by exposure to sunlight. The dose is the same as ordinary santonin and it is stated to be useful in sprue and dysentery. **Trochiscus santonini** contains 1 grain in each. Dose 1 to 3. **Trochiscus santonin Co.** contains $\frac{1}{2}$ grain of santonin and calomel each. Dose 1 to 2 grains.

Confectio santonini Co. containing santonin in combination with ginger, jalap, sulphur and senna is used in some of the children's hospitals.

Haustus santonini et olei ricini, contains 4 grains of santonin, half an ounce of castor oil, half an ounce of mucilage and peppermint water. It is prescribed on an empty stomach but symptoms of poisoning may occur.

Sodii santoninas. Dose $1/50$ grain (1 mgm.) cautiously increased to $1/20$ or $1/10$ grain (3 to 6 mgm.) is used for systemic effects. As an anthelmintic $1/4$ to 1 grain for adults preferably in salol-coated pills.

Calci santoninas (N. O.). Dose 1 grain. It is a white tasteless insoluble powder.

Artemisine in doses of $1/600$ grain (0.0001 gm.) has been used as a gastric stimulant.

CHAPTER VI

ANTHELMINTICS ACTING ON NEMATODES (*Contd.*)

THYMOL AND ALLIED COMPOUNDS

A number of compounds belonging to the stearoptene group, including menthol, borneol, camphor, and thymol have been tried as anthelmintics but only the last-named is effective. Caius and Mhaskar (1924) showed that so far as these compounds are concerned, (a) the hydrogenation of benzene decreases their anthelmintic action, but increases their toxicity to the host, (b) the total destruction of the benzenoid structure leads to the formation of toxic compounds with no anthelmintic properties, (c) esterification of the phenolic hydroxyl group leads to formation of non-anthelmintic and non-toxic compounds, e.g., thymotal.

THYMOL.

Thymol was first tried in the treatment of hook-worm infections by Bozzolo in 1879. Since then it has been extensively used with satisfactory results. In recent years, however, oil of chenopodium and carbon tetrachloride have largely supplanted this drug, for they are more effective and less dangerous than thymol and can safely be used for mass treatment and labour forces.

Thymol or thyme camphor is contained in a number of essential oils from many plants, the chief amongst which is *Thymus vulgaris*, an evergreen shrub belonging to the Labiatae family. In India thymol is manufactured on a commercial scale from *Cuminum cyminum* which contains large quantities of cumin oil whose chief constituent is cumin aldehyde which can be readily converted into thymol. The oil of *Carum copitum* known as oil of *ajowan* also contains not less than 40 to 50 per cent. of thymol. The oil from *Monarda punctata* growing in America contains 60 per cent. of thymol and *Origanum hirtum* growing in Crete contains 60 to 67 per cent.

Chemistry. The chemical formula of thymol is methyl-isopropyl-phenol and it is a stearoptene. It is a higher homologue of benzene. It occurs in large transparent crystals, slightly soluble in water (1 in 900) but freely soluble in fats, oil and alcohol. When it comes in contact with menthol, chloral, camphor, etc., it liquifies them.

Pharmacological action. The action of thymol is similar to that of phenol; it has about one fourth the antiseptic power of phenol and in concentration as low as 1 in 10,000 kills free-living protozoa such as paramoecia. It is fatal to staphylococcus aureus in 0.5 per cent. concentration, to typhoid and anthrax bacilli in 0.8 per cent. and pneumococcus in 1 per cent. Growth of putrefactive bacteria is prevented by 0.1 per cent. solution and 1.0 per cent. is required to kill them. It inhibits the growth of moulds in 0.02 per cent. solution.

Externally thymol has no action on the unbroken skin but it can exert its caustic or irritant action on mucous membranes. When taken internally in ordinary anthelmintic doses, it produces a feeling of well-being and comfort in the stomach; there is reflex stimulation of the peristaltic movements of the intestines. The presence of fatty constituents in the intestines promotes absorption of thymol and if this absorption is large it gives rise to systemic effects and may produce fatty degeneration of the liver. It is, therefore, advisable to avoid fats, alcohol, glycerine, etc., when thymol is being administered.

Small doses of thymol administered orally produce reflex stimulation of the heart and the respiratory centre; large doses produce a marked depression and finally paralysis. The central nervous system is always affected to a certain extent. There is at first a slight stimulation of the cerebral cortex followed by depression which gives rise to narcotic effects. Headache, buzzing in the ears, dizziness, lowering of the body temperature and collapse follow when large quantities are absorbed.

Given by the mouth in doses of 15 to 30 grains (1 to 2 gm.) most of the thymol is absorbed for none is found in the faeces. About half of the drug ingested is excreted in the urine partly in combination with sulphuric and glycuronic acids, partly unchanged and partly oxidised to a bivalent phenol-thymol hydroquinone. The greenish tint so often noticed in the urine after administration of thymol is due to the presence of this substance. The kidneys are irritated after large doses and albuminuria may result. When given in excessive doses it is also excreted in the bronchial mucous membrane and may produce inflammation of the lungs. The drug has no direct effect on the uterine movements but it may reflexly stimulate them by irritating the pelvic viscera.

In vitro thymol has a powerful action on earthworms. In 1 in 2,000 solutions the worms show signs of irritation and their movements are markedly increased at first, but they are soon paralysed and die in 10 to 15 minutes. In 1 in 10,000 solution they are killed in $1\frac{1}{2}$ hours; and

1 in 20,000 they are rapidly paralysed but are not killed. Hookworms are killed by weak solutions of the drug.

Anthelmintic effects. There is no unanimity of opinion about the effective dose of thymol. Some authors have recommended as much as 120 to 150 grains in divided doses of 25 to 30 grains, while others consider such large doses are neither necessary nor justifiable. They do not advise more than 60 grains of thymol in a day and recommend not to repeat it in less than a week. In pregnant women the dose should not exceed 30 grains, and in cases of extreme debility from old age, heart disease, chronic diarrhoea and dysentery the dose should be small and divided. The drug should at once be stopped if untoward symptoms appear. Ashford and King recommend the following scale of dosage:—

Under 5 years 8 grains (0.5 gm.) ; 5—10 years 15 grains (1.0 gm.) ; 10—15 years 30 grains (2.0 gm.) ; 15—20 years 45 grains (3.0 gm.) ; 20—60 years 60 grains (4.0 gm.) ; over 60 years 30—45 grains (2 to 3 gm.).

It is customary to give the drug in two or three divided doses, of 15, 20 or 30 grains each at intervals of 1 to 2 hours followed by a strong saline purgative. It is better not to give coarse crystals as these are likely to pass through the bowels unchanged, probably without coming in contact with the parasites. The drug also has a tendency to pack together in hard lumps if given in capsules and it is preferable to give it mixed with sugar of milk or bicarbonate of soda. In case of children who are not capable of swallowing capsules, thymol is best given in powdered form suspended in simple syrup or mixed with chocolate.

The preparation of the patient is important when thymol is being given as an anthelmintic. The following procedure is recommended (Ashford).

The patient is given a light meal and one ounce of saturated solution of magnesium or sodium sulphate the night before. At 8-30 a.m. the following morning 30 grains (2.0 gm.) of powdered thymol are given in capsules; at 10 a.m. another similar dose is given; at 11 or 12 o'clock, 1 ounce of saturated solution of magnesium sulphate is given. No break-

fast is allowed and food is only permitted after the bowels have moved. The patient should remain in bed and should use a bed pan.

Thymol is the classical drug for the treatment of hookworm infections, but more than one course of treatment is often required to produce a cure. In Ashford's series 68.6 per cent. were cured in 30 days and 94.4 per cent. in three months (presumably 4 to 8 treatments). He is of opinion that the drug is more effective against mature worms. Fourteen to fifteen days after infection the worms develop a buccal capsule and attach themselves to and feed on the mucous membrane. From this time onward they are exposed to the action of the drug and treatment should then be given. Darling, Barber and Hacker succeeded in removing 95.7 per cent. of necators and 57.9 per cent of ankylostomes with a single dose of 60 grains (4.0 gm.) of thymol. Even with such large doses as 180 grains (12.0 gm.) the drug is less effective against ankylostomes than other available anthelmintic. Clayton Lane (1928) still regards it as the best anthelmintic against hookworm, since even after 60 grain doses no death occurred in his series.

The effect of thymol on other intestinal nematodes is distinctly inferior to its effect on hookworms. *Ascaris*, *trichuris* and *oxyuris* are not very vulnerable to its action. Tapeworm segments are expelled but the removal of the heads is very doubtful. Thymol has also been used in trichiniasis and the parasites are expelled when they are present in the gut. Good results have also been obtained even when the parasites have lodged in the muscles. A 6 per cent. solution of the drug in oil has been given intramuscularly in doses of 2 to 3 c.cm., injections being given daily. No toxic symptoms are observed and there is marked improvement in the patient's condition. Trichiniasis can be prevented if treatment *per os* is begun within 24 hours of the ingestion of infested meat, with 2 grains (0.13 gm.) of thymol repeated three or four times and followed by a purge.

Other uses. Thymol in concentrations of 1 grain in an ounce is used for spraying the nasal mucous membrane in catarrhal affections. For general disinfection a solution of 1 in 200 (one tablespoonful in 5

pints) should be used; thymol has also been used as a paint in ring-worm, eczema and various skin diseases. In amoebic dysentery considerable benefit is obtained by colonic irrigation with 1 in 2,000 solution in conjunction with emetine bismuth iodide. In flagellate diarrhoea, an enema with 1 in 2,000 solution and 4 to 8 grains (0.25 to 0.5 gm.) of thymol by the mouth are recommended. A 5 per cent. solution in alcohol and 2.0 per cent. in cinnamon oil is used as a paint to control infestations of the skin by fungi. One to 2 grains (0.06 to 0.13 gm.) are given 3 or 4 times a day in typhoid fever with tympanitis.

Toxic effects. In large doses thymol produces symptoms resembling carbolic acid poisoning. There is usually acute pain over the epigastrium, due to the caustic and irritant action of the drug on the mucous membrane of the stomach; nausea and vomiting follow and the patient becomes prostrated. Giddiness, roaring sounds in the ears, drowsiness, etc., commonly occur; there is often salivation and cyanosis, and the patient may become unconscious. The temperature has a tendency to fall below normal and both the pulse and respiration are slowed; skin rashes may appear; the urine may become scanty; abortion may follow in pregnant women. With very large doses collapse may be rapidly produced and death may occur in a few hours. The intensity of symptoms depends on the amount absorbed, and the presence of solvents like fats and alcohol strongly increases the tendency to produce intoxication. A purgative given a few hours after the drug prevents intoxication by washing it out of the gut. Sometimes the intoxication is delayed and sets in several days later when all the symptoms except weakness have disappeared.

Treatment of poisoning. The stomach should be rapidly washed out with warm water. Demulcents may be given to prevent corrosion of the mucosa. Cardiac and respiratory stimulants, *e.g.*, 1/120 grain (0.005 gm.) of atropine and 1/30 grain (0.002 gm.) of strychnine should be given. Hot coffee is useful in overcoming weakness. Alcoholic stimulants and tinctures are contraindicated.

Precautions and contra-indications. Thymol should be given with caution when there is anæmia, nephritis, advanced cardiac disease, pregnancy and debility due to old age. Patients suffering from chronic diarrhoea and dysentery also take it badly.

Thymotal. Attempts have been made to lower the toxicity of alkyl phenols by converting them into non-irritant esters, such as carbonates, carbamates, etc. Thymotal or thymol-carbonate is prepared by passing phosgene gas through a concentrated solution of thymol in an aqueous solution of caustic soda. It was at one time considered to be a very effective remedy against ankylostomes, but later it was found to be absolutely useless even in 40 grain doses. Although these esters are broken up in the alimentary tract by hydrolysis forming the original hydroxyl compounds, they do not attain sufficient concentration to be effective anthelmintics.

Isothymol or carvacrol was synthetically prepared from turpentine during the Great War when the supply of thymol from Germany was stopped. Chemically carvacrol is an isomer of thymol and its pharmacological action bears a close resemblance to thymol in many respects. The anthelmintic action of carvacrol was tested by Sollmann on earthworms with fairly satisfactory results. The International Health Board reported unfavourably on its efficiency against hookworm. Caius and Mhaskar (1924) tried carvacrol in 20–60 minims. doses with promising results. They found it to be a good anthelmintic but decidedly inferior to thymol. It is also more irritant and somewhat more toxic than thymol.

Preparations.

Thymol disinfectant (Martindale). It is a potent antiseptic; when employed as a general disinfectant, 1 in 200 solution in water should be used.

Liquor thymol is made of 1 part of thymol in 800 parts of warm water; used as an antiseptic gargle well-diluted.

Mistura oleobalsamica. Dose is 1 to 4 drachms in water as a carminative stimulant.

Pastilli thymol. Contains 1/32 grain of thymol in each.

Pigmentum thymol. It consists of thymol 1 part, ether 10 parts and spirit 5 parts or may also be prepared with petroleum oil; useful in ringworm of the scalp.

Thymaglycine. It is a palatable preparation containing sodium benzoate, menthol, essential oils, glycerine and thymol water. It is given in rhinitis, pharyngitis, quinsy, etc., or as a spray for throat and nostrils, diluted 1 to 3 in water. For colitis in children 5 to 10 min. in paraffin or water are given.

Glycethymellae. It consists of potassium carbonate, sodium benzoate, sodium borate, sodium salicylate, thymol, menthol, glycerine and alcohol coloured with cochineal. It is frequently prescribed as an intestinal antiseptic in doses of $\frac{1}{2}$ to 1 drachm and also as a gargle.

Unguentum thymol. Prepared in strength of 20 grains (1.3 gm.) in an ounce of soft paraffin useful in eczema. A compound ointment has boric acid and zinc oleate in addition.

Thymol carbonate (Thymotal). It is a colourless and tasteless crystalline powder employed in ankylostomiasis in doses of 5 to 15 grains (0.3 to 1.0 gm.).

Thymoform is obtainable in the form of lozenges containing thymol and formic aldehyde in a cane-sugar basis.

BETA-NAPHTHOL

Beta-naphthol has been used as an anthelmintic for quite a long time. As early as 1904, Bentley used the drug against hookworm in Assam and later in 1908, Burkitt and Drummond tried it with excellent results. The chief merits claimed on its behalf are that it is not unpleasant to take, it is more satisfactory for routine use and is one-tenth the price of thymol. Caius and Mhaskar reported very favourably on the drug and recommended it as the safest and most efficacious anthelmintic for hookworms, but subsequent work has failed to substantiate their claims. With the advent of carbon tetrachloride and oil of chenopodium beta-naphthol is gradually receding from the field though it is still used in some places.

Source and composition. Naphthol is derived from the hydrocarbon naphthalene by the substitution of a hydroxyl for one of the hydrogen atoms. There are two naphthols—the alpha- and the beta-naphthols—the former is very toxic and is not used in medicine.

Beta-naphthol occurs in colourless glistening crystals of pale buff-coloured lamellæ. It has a faint phenol-like odour and has a pungent hot taste; it is very slightly soluble in cold water but dissolves readily in boiling water. The drug is of uniform quality and does not readily change or deteriorate though it is better kept in amber-coloured bottles.

Pharmacological action. Externally beta-naphthol is irritant to the unbroken skin and may be absorbed therefrom producing toxic symptoms. It produces inflammation and corrosion of mucous membranes and raw surfaces. Beta-naphthol can be taken by healthy individuals in fairly large quantities without producing any untoward symptoms. As a rule, a slight degree of warmth is felt in the stomach, but there is no burning pain, nausea and vomiting as in the case of thymol. Beta-naphthol is sparingly soluble in saliva and in the gastric juice, hence its absorption from the stomach is slight; it is more readily absorbed from the small intestine. The peristaltic movements of the intestine are increased and some purging results. Large doses produce an irritant action on the gut and produce nausea and vomiting.

The heart is reflexly accelerated at first, but later it becomes slower which is due to direct action on the cardiac muscle. In large doses, it

has a toxic effect on the red blood corpuscles, especially in patients with active or latent malaria. The corpuscles may be destroyed in sufficient quantities to produce hæmoglobinuria, jaundice, and severe anaemia.* Large doses depress the respiration probably from depression of the respiratory centre. Therapeutic doses have no effect on the central nervous system, but after absorption of large amounts, it produces giddiness and convulsions followed by paralysis and coma. Changes in the retina and opacity in the lens have been produced in some cases, after its use.

Beta-naphthol is rapidly excreted in the urine and during its excretion it may produce inflammation of the kidneys, even when the doses taken are not large. It is excreted in combination with glycuronic and sulphuric acids and imparts to the urine a dark brown or mahogany red colour. Although salivation is produced, it is not excreted in the saliva.

Anthelmintic effect. There is great diversity of opinion about the toxicity and efficacy of beta-naphthol as an anthelmintic. The dosage recommended varies from 30 to 90 grains (2.0 to 6.0 gm.), on three successive days until the total quantity has been given. Such large doses often produce destruction of the red blood corpuscles; doses of 30 grains (2.0 gm.), on the other hand appear to be too small. According to Caius and Mhaskar, the drug is quite safe and effective in doses of 50 grains (3.3 gm.) in a single dose, and 60 grains (4.0 gm.) divided into two doses. There is again no definite rule about the use of the pre-purge. The omission of the preliminary purge is not attended by any fall in anthelmintic efficiency and the after-purgative is often unnecessary in as much as the drug itself has got a purgative effect. It is, however, better to use both the pre- and post-purgative, for this procedure decreases the chances of production of untoward effects.

Beta-naphthol has been found by nearly all workers with the exception of Caius and Mhaskar to be less efficient than thymol, and certainly less so than oil of chenopodium or carbon tetrachloride. Usually at least four or five treatments are necessary before a cure is effected. Its action on ascaris and trichuris is no more promising than its action in hookworms. Smillie in Brazil removed only 52 of 124 ascaris (41 per cent.) as compared with 91 per cent of 454 cases removed by chenopodium. *Tenias* are also very little affected by it.

Toxic effects. The toxicity of naphthalene bodies in man varies widely. Naphthalene has been taken in 75 grain (5.0 gm.) doses without ill effects, while much smaller quantities have produced severe gastroenteritis. Deaths have been reported from the external use of a mixture of 1 part of beta-naphthol and 2 parts of camphor. In man, restlessness followed by convulsions and coma with stertorous breathing, have been seen even in non-fatal cases. Naphthalene and beta-naphthol are toxic drugs, 2 drachms (8 gm.) causing death in a rabbit; in the dog the fatal dose is 1.0 gm. per kilo.; cats die of convulsions after 1.5 grains (0.1 gm.). Large doses produce a burning sensation in the epigastrium, diffuse abdominal pain, nausea, vomiting, diarrhoea, or even dysentery-like symptoms, spasm of the face muscles, weakness and fever. Micturition is painful, the urine becomes very dark, scanty, and shows the presence of bile, albumen and casts; suppression of urine may supervene, producing uræmia. The spleen, the liver and the kidneys are enlarged and hyperæmic, and the gall bladder is distended. Death may occur from convulsions or gradual failure of respiration, the heart goes on beating after the respiration has stopped. All these symptoms are more readily produced in malarial patients. The Porto Rican Anæmia Commission tried the drug extensively and found that 83.3 per cent. of their cases who took it suffered from albuminuria. Cairns and Mbaskar (1921) noted that all their cases of albuminuria and hæmoglobinuria occurred with doses over 60 grains administered for several days. With small doses no such symptoms were produced.

Precautions and contra-indications. The urine of patients should be always examined before administering the drug, and if the kidneys are damaged it should be given with caution. Large doses should not be given to those who are suffering from or have suffered from malaria.

Preparations.

Naphthol (B.P.) and beta-naphthol (U.S.P.X.). Dose 15 to 30 grains (1 to 2 gm.), but 40 to 50 grains in single or divided doses is considered quite safe. It is usually given in the form of cachets or pills or in the form of an emulsion in oil. **Betol or beta-naphthol salicylate (N.O.)** has no anthelmintic action. Dose 4—8 gr., used in the form of cachets or pills or as emulsion in milk in rheumatism, cystitis and intestinal catarrh. **Benzonaphthol or beta-naphthol benzoate (N.O.)** has also no vermifugal action, used as diuretic and intestinal antiseptic. Dose 15 grains (1.0 gm.). **Beta-naphthol petroxalin (N.F.)** 10.0 gm. of beta-naphthol dissolved in 90 gm. of liquid petroxalin used as a parasiticide application. **Naphthalenus (N.O.)** has been tried against hookworm but has no anthelmintic action. Dose the same as beta-naphthol. **Naphthalene tetrachloride** was tried in 8 grain (0.5 gm.) cachets every 4 hours in colitis.

RESORCINOL DERIVATIVES

A number of synthetic compounds have been prepared and some, the isohexyl derivatives of either resorcinol or phloroglucin, are promising.

HEXYLRESORCINOL

Hexylresorcinol is 1 : 3 dihydroxy - 4 - hexylbenzol. It is a white, waxy, crystalline substance and is quite stable. It is sparingly soluble in water (1 in 1,700) but it readily dissolves in alcohol, ether, chloroform and vegetable oils. Hexylresorcinol is considered to have highly germicidal properties, the phenol co-efficient varying between 46 and 52. It has been used as a mouth wash, gargle, nose and throat spray in concentration of 1 in 4,000. It has been administered in gelatine capsules in doses of 0.45 to 0.6 gm. three times a day, as an urinary antiseptic. The drug has been continued for as long as ten weeks without showing any deleterious effects. For children, a 2½ per cent. solution of the drug in olive oil under the name of Caprokol (N.N.R.) has been prescribed two or three times a day. It has been highly spoken of in cystitis and pyelitis and appears to be well tolerated.

Pharmacological action. Crystalline hexylresorcinol has irritant properties and is liable to produce a burning sensation in the mouth. The irritating property of the drug can be overcome by dissolving it in olive oil but this reduces its vermifugal power. A solution of 0.1 per cent. of hexylresorcinol *in vitro* killed pig ascaris in 2 minutes while it took more than 20 minutes to be effective in 3 per cent. olive oil solution. Repeated administration to dogs is known to have produced petechial hemorrhages in the buccal and gastric mucous membranes. The drug is, however, precipitated by proteins, and probably on this account it does not penetrate deeply into the tissues. When given with alcohol absorption is facilitated. Experiments on dogs show that about 27 per cent. of hexylresorcinol taken by the mouth is excreted in the urine and 67 per cent. is eliminated in the feces.

Anthelmintic properties. The anthelmintic property of the drug has been noticed only recently. Lamson and others in America were the first to study the effect of hexylresorcinol as an anthelmintic. They found that the drug in large dilutions was lethal to pig ascaris *in vitro*. It removed 100 per cent. of the ascaris in 16 out of 17 dogs as shown by autopsy, and it removed 90 to 100 per cent. of these parasites in 20 patients when given in 1 gm. doses in gelatin capsules. This was

followed later by more systematic investigation by Lamson, Caldwell, Brown and Ward (1931) into the effectiveness of the drug in human ascariasis. They administered the drug in hard gelatin capsules to avoid the local irritant effect, the maximum dose being 1.0 gm. for adults, magnesium sulphate being given two hours after. They succeeded in curing 7 out of 10 cases; the egg reduction amounted to 96.4 per cent. in a total of 5 cases, all of whom were cured. The reduction was cent. per cent. if the purgative was deferred for 24 hours. Food, shortly before or after the treatment, greatly reduces its efficacy. Similar results were obtained by Lamson and his co-workers in field work in ascaris infection. They also tried the drug in hookworm infestation of children and egg-reduction was 80—90 per cent. with a single dose. Lamson and his co-workers (1932) in evaluating the comparative results of hexyl and heptylresorcinol considered the former to be a better anthelmintic. In hookworm infection, in a total of 25 cases given doses of 1 gm., the average egg-reduction was 62.7 per cent. but none was cured. In ascariasis, in doses varying from 0.8 to 1.0 gm., the cure rate was 29.4 per cent. and the average percentage of egg reduction was 73.5. Lamson, Brown and Ward (1932) consider a single dose of hexylresorcinol to be capable of removing more than 90—95 per cent. of ascaris, 80—85 per cent. of hookworms and 40—45 per cent. of trichuris. Brown (1932) calls attention to the possibility of reaction taking place between gelatin and hexylresorcinol when given in capsules, especially in hot moist climate. He advocates sugar-coated pills in dosage of 0.1 gm. per year of age up to 10 years and 1.0 gm. to every one above this age. The treatment was started in the morning the drug being given in an empty stomach, and food was withheld for 4 to 5 hours afterwards. The average egg-reduction was 90 per cent. of ascaris and 32 per cent. of trichuris. Two doses of hexylresorcinol with an interval of 3 weeks between the courses, reduced the ascaris egg count to 96 per cent. and the rate of cure was about 93 per cent. Maplestone and Mukherjee (1932) using the drug in hard gelatin capsules, under strict fasting conditions, obtained a cure rate of 66.6 per cent. and an egg-reduction of 94 per cent. in 21 cases. In hookworm infestation in 26 cases the corresponding figures were 7.7 and 71.4. In ten cases of taeniasis no head was recovered after giving the drug but five reported no recurrence 3 months later. Biggam and Ghalioungui (1932) treated 50 cases of *ankylostoma duodenale* and only 26 patients were found to be free from the parasites even when repeated administration of as much as 2 gm. were employed. The drug did not produce any toxic symptoms, but the results were far less encouraging than with other available anthelmintics.

Method of administration and dosage. Before administering the drug, proper dietary preparation is necessary. In the evening previous to the commencement of the treatment, only

milk and bread should be given. Early next morning hexyl-resorcinol is given in hard gelatin capsule in doses of 1.0 gm. with about 2 ounces of water to help in swallowing the drug. No food is allowed for 4 to 5 hours and alcohol is forbidden. Reaction between the drug and gelatin can be avoided if the capsules are filled immediately before they are administered. Sugar-coated pills each containing 0.2 gm. are available and they are unaffected by climatic conditions. They are quite convenient to use except that in children they may cause a superficial burn in the mouth if they are chewed, on account of the protein-precipitating property of the drug when it comes in contact with the mucous membrane. In the majority of cases, hexylresorcinol exerts a cathartic action and the patient has five or six watery stools after it. A dose of magnesium sulphate should however be given next morning, *i e.*, 24 hours after the dose. The toxic symptoms observed are negligible. Some of the patients may complain of pain in the epigastrium but this is very rare, even with doses as high as 2 gm. for a single administration. Repetition of the dose even at short intervals in maximum quantity does not produce any toxic symptoms. Hexylresorcinol, so far as is known has proved of value in ascariasis; in ankylostomiasis and other helminthic infection its superior efficacy over other drugs has yet to be worked out. Probably in hookworm infection, in anæmic and debilitated subjects it may be a safer drug than the other remedies in use.

HEPTYLRESORCINOL

On account of the results of hexylresorcinol in the treatment of helminthic infestations other alkyl resorcinols have also been used. Heptylresorcinol is one of them. Locally, it produces a smarting burning effect on the tongue and is irritant to the buccal and gastric mucous membrane. About 80 per cent. of heptylresorcinol is excreted in the faeces. Lamson and his co-workers (1932) in a comparative study of the effect of the two resorcinols in helminthic infections found that hexylresorcinol seemed more effective against hookworm, ascaris and trichiuris than heptylresorcinol. The average egg-reduction in hookworm disease with 1.0 gm. doses of heptylresorcinol was 55.2 per cent., in ascaris 78.5 per cent. and in trichiuris 35.8 per cent. Mackie (1931) using sugar-coated pills containing 0.15 gm. found that none of the intestinal protozoa were affected by the drug with the exception of *Iodamoeba butschlii* and

Giardia intestinalis. Thonnard-Neuman (1931) reports that cases of hookworm infestations proved refractory towards heptylresorcinol dissolved in olive oil. David and Johnstone (1933) treated 23 cases of hookworm infection with the drug; six were treated with olive oil solutions of heptylresorcinol, but this proved ineffective. The crystalline drug in gelatin capsules was later tried, which proved partially successful; trichiuris infection proved refractory.

Heptylresorcinol is generally given in hard gelatin capsules in doses of 1.0 to 1.5 gm. preferably in the morning on an empty stomach and food is withheld for 4 to 5 hours. Solution of the drug in olive oil greatly lowers its efficacy. A purgative should be prescribed several hours later. The drug has also been prescribed in gelatin capsules coated with salol. This prevents liberation of the drug in the stomach so that it may reach the parasites in the intestine in an effective concentration. The results of treatment are more favourable in hookworm infection than in ascariasis or tapeworm infestations.

Preparations.

Hexylresorcino'ls (tablets 0.2 gm.), **Liquor Hexylresorcinolls** (1 in 1,000).

CHAPTER VII

MISCELLANEOUS ANTHELMINTICS

Intestinal antiseptics. Some of the compounds which show well-marked disinfectant properties in the gastro-intestinal tract, such as thymol and beta-naphthol, have proved excellent anthelmintics. This observation opened up the possibility of other intestinal antiseptics behaving in a similar manner. With this idea in view, a number of reputed intestinal antiseptic drugs have been tried to determine their vermifugal properties. It has been found, after a large series of experiments conducted by workers in different parts of the world, that these drugs, with the possible exception of some of the propenyl derivatives of phenol and salicylic acid esters, are useless as far as their anthelmintic activity is concerned. Some of these are positively dangerous to the host instead of being in any way inimical to the parasites.

Potassium permanganate in maximum doses, bismuth carbonate, kaolin, naphthalene, phenocoll, methylene blue, guaiacol carbonate, creosote, izal, salicylic acid, salol, acetyl-salicylic acid (aspirin), salicylic ester of beta-naphthol (betol), the crude phenols, etc., have all been tried and found to be useless.

Methyl salicylate, a volatile ester of salicylic acid has, however, well-marked vermifugal properties. In doses of 30 to 60 min. (2 to 4 c.cm.) it has been found to be very effective against hookworms, but has little or no effect on ascaris and trichuris. Methyl salicylate is present in oil of wintergreen (*oleum gaultheria*) in large quantities (99 per cent.). It has been given in 30-60 min. doses with castor oil and gum acacia with satisfactory results.

A number of propenyl phenols occur in nature, *e.g.*, anethol, eugenol, etc. These are fairly good anthelmintics and do not possess the toxic properties on the host, of the crude phenols.

Purgatives. These drugs have got very little vermifugal action but they irritate the gastro-intestinal tract and in this way bring about a vermifugal effect. Magnesium sulphate, calomel, phenolphthalin, *oleum ricini*, *oleum tiglii* and aloes have all been tried at some time or other by different workers, but they have no vermifugal properties. Whipworms (*trichuris*) have been successfully treated with two ounces of castor oil on four successive days, followed by an enema of 2 litres of 0.5 per cent. solution of sodium carbonate with one ounce of kaolin added to it. The patient is kept on a low diet and is also given one ounce of kaolin daily on each of these days. After four days of treatment the enema is continued for two days more.

Heavy metals. A number of other drugs have been used for their anthelmintic effects in man and animals. Copper sulphate has chiefly been used in veterinary practice, especially in infection with *Hæmonchus contortus*, the stomach worm of sheep. The arsenical compounds such as stovarsol have been given but their vermifugal effect is doubtful. Injections of organic arsenicals and tartar emetic have been found to have some effect on *clonorchis* infections in man. Salvarsan and sulpharsenol injections have been given in oxyuris and guineaworm infections with success in some cases. Mercurochrome has been given intravenously against *Schistosoma japonicum* in man in 1.0 per cent. solution, with some degree of success.

Embellia ribes and **E. robusta** family Myrsinaceæ, had the reputation of vermicidal action, but Caius and Mhaskar (1923) showed them to be quite ineffective against hookworms, round worms and whipworms. The chief constituent of the fruit is embelic acid, which occurs in golden-yellow crystals, resin and tannin. Anthelmintic dose 1 to 4 drachms (4 to 10 gm.) of the powdered drug.

Azadirach. The bark and root of *Melia azadirachta* has been used as an anthelmintic against roundworms. The active constituent of the drug is margosic acid and a resin. In India and in the southern United States, the fresh bark of the root is employed to expel ascaris. The powdered bark is given in doses of 20 grains (1.3 gm.), or the decoction (made by boiling 2 ounces of the bark in a pint of water until reduced to half) is given in one tablespoonful doses hourly or every second or third hour; a purgative is given after the second or third dose. The oil has no anthelmintic properties. In excessive quantities the drug produces dizziness, purging and collopse.

Corsican moss (helminthochortan) is a mixture of various marine algæ and is used in France and Italy to expel ascaris. It is best given as a sweetened decoction with milk in a single dose before breakfast. Dose for a child under two years is 15 to 45 grains (1 to 3 gm.); of 10 years 3 to 4 drachms (12 to 15 gm.). It is sometimes combined with santonin or santonica.

Mucuna or Cowhage is the fruit of *Mucuna pruriens* a climbing plant of tropical America. The pod is covered with stiff hairs which produce intense itching. Cowhage acts mechanically, the hair piercing the parasites. The pod is dipped in molasses and the hairs are removed by scraping. Dose is one teaspoonful for a child and one tablespoonful for an adult. The drug has been used both against roundworms and tapeworms, but it is too disagreeable to take and too uncertain in its action.

Butea frondosa has been used as an anthelmintic against roundworms but opinions differ regarding its efficacy. The seeds have been analysed and they contain 16 per cent. of a fixed oil called *moo-dooga oil*, small quantities of resin and large quantities of a water-

soluble albuminoid. There are no active principles of the nature of alkaloids, neutral principles or glucosides. The powdered seeds have been used as an anthelmintic in doses of 30 to 60 grains (2.0 to 4.0 gm.), but they are unpleasant to take and often produce pain in the stomach, vomiting and giddiness. The oil and the resin were separately tested against hookworm and ascaris. The alcoholic extract, the oil and resin had no effect, but freshly powdered seeds produced good results in ascaris infection. Old worm-eaten seeds met with on the market are inactive.

Ficus laurifolia has been recommended as an anthelmintic against whipworm in man in doses of 15 to 30 gm. The latex of this plant has definite anthelmintic properties and is worthy of trial. The active principle is unknown though it probably resides in the solid portion of the latex. In its natural state, the latex forms a perfect emulsion of rubber and resinous substances; it contains an albumin and substance of fixed composition yielding ammonia, which is probably responsible for its anthelmintic activity. The latex unfortunately readily ferments and will only keep for 4 to 5 days, though in an ice box it has been kept for several months. The drug is very effective against whipworms (*Trichuris trichiura*). It may produce toxic symptoms, colic, nausea, vomiting, muscular cramps, delirium, syncope, urticaria, rectal and vesical spasms, and partial suppression of urine.

Quassia is the wood of the trunk and branches of *Picraena* or *picroasma excelsa*. *Picroasma quassioides* Benn is a common shrub growing in the sub-tropical Himalayas. The active principles of quassia are substances called picrosmin and quassin.

Quassia is poisonous to many insects and is used as an insecticide. It has been used as an anthelmintic against threadworms for a long time. Kennard (1915) tried quassia in ankylostomiasis without success but Barnes (1915) claims to have cured 70 per cent. of cases with the drug. Caius and Mhaskar by giving 5 ounces of an infusion of the drug prepared by adding 1 ounce of finely powdered root to a pint of boiling water, failed to cure any case. It has, however, been found effective in threadworms especially in children; generally the decoction is given in the form of an enema, but quassia suppositories containing $\frac{1}{2}$ grain (0.016 gm.) of the extract with a gelatin basis, may also be prescribed. Two grains of the extract of quassia in the form of a pill taken three times daily along with some purgative are also given to clear out threadworms.

Spigella marilandica or pinkroot is a plant belonging to the family Loganiaceae which is widely spread all over the southern parts of the United States. It was formerly considered as a powerful anthelmintic especially against ascaris.

The constituents of the root are *Spigelline*, which is a volatile alkaloid resembling nicotine and conine, a bitter principle soluble in water, a volatile oil and resin.

Very little is known about the action of this drug. The alkaloid is a gastro-intestinal irritant, and in poisonous doses it produces convulsions. It is absorbed slowly from the gut and if combined with a purgative it does not produce any toxic effects. Sollmann (1918) tested its activity on earthworms but his results were not promising. Pink-root is chiefly used as a vermifuge against roundworms and is said to be quite effective against them. Careful experiments on animals have shown that it has no marked anthelmintic action against any of the parasites.

Chrysanthemum cinerariæ. The active principle is said to be a good parasiticide, it is non-toxic and non-irritant. It is said to be useful in ascariis, trichuris, threadworm and tapeworm infections.

Rhumnus cathartica. A syrup made from the berries with jalap is said to be useful in oxyuriasis.

Allium sativum. The allyl compounds contained, produce complete paralysis of ascariis *in vitro*, but their anthelmintic effects in man are doubtful.

Geraniol in doses 0.3 c.cm. per kilo. body weight has been tried in dog but has no effect. Various species of *Cambretum* occurring in Brazil, extracts of *C. quadrangulans*, essential oils of *Tageterminulus* and *Kyllinga odorata* were quite ineffective.

Acalypha indica, petroselinum sativum and **quilsqualis indica** have no anthelmintic properties.

Rotylon. It is an aromatic combination, insoluble in water, but soluble in alkalies, manufactured by Bayer Meister Lucius Ltd. The drug is set up in capsules each containing 0.4 gm. When taken in liquid form it produces a burning sensation in the tongue which is followed by one of prolonged anæsthesia. The anthelmintic properties of this drug are under investigation.

Vernonia anthelmintica. Powdered seeds in doses of 30 to 60 grains have a weak vermifugal action against ascariis and a more powerful action against oxyuris. The bitter substance isolated, in doses of 3 to 10 grains, has a weak vermifugal action against ascariis and a decided action against oxyuris. When combined with calomel and followed by magnesium sulphate the vermifugal action is considerably enhanced. The drug has no action whatsoever against the hookworm and tapeworms. The anthelmintic properties of the drug against ascariis and even against oxyuris are weaker and in no way comparable with some of the other compounds now in the British Pharmacopœia.

CHAPTER VIII

ANTHELMINTICS ACTING ON SOMATIC PARASITES

Although this subject is of very great importance very little is known about it. The absorption of the drug is essential for any action to be produced on blood and somatic worms, and since most of the anthelmintic remedies are toxic to the host when absorbed in more than very small quantities, the difficulty of finding a suitable drug to destroy the parasites is great. Helminthic parasites may occur almost in every organ and tissue in the body, and some are more easily reached than others. The parasites lying in the liver are easy to reach since the drugs absorbed from the gut go through this organ first, and they reach it in high concentration. The parasites lying in the lungs can be reached by drugs given by inhalation, and parasites in the blood can be reached by drugs from the digestive tract or by injection. Parasites lying in the subcutaneous tissue, muscle, central nervous system, etc., must be reached indirectly by drugs circulating in the blood stream, which are therefore much diluted by the time they reach the parasites.

The principal human somatic or extra-intestinal parasites important from point of view of anthelmintic treatment are, (1) flukes, parasitic in the liver, bile ducts, or pancreatic ducts; (2) lung flukes; (3) schistosomes located in the mesenteric blood vessels; (4) tapeworm cysts in muscles, liver and other viscera and the central nervous system; (5) filariae situated in lymph glands or ducts. The embryos of trichina worms during their wanderings in the blood stream and muscle tissue, before encystment in the muscle fibres may also be considered capable of anthelmintic treatment.

The drugs which are considered effective against these parasites are practically the same as those used against intestinal helminthic infections. During recent years a few more drugs have been added to the list, *e.g.*, antimony compounds, emetine, carbon tetrachloride, etc. The anthelmintic properties

of these drugs will be considered separately. The anthelmintic treatment of somatic infections can best be considered from standpoint of the groups of parasites.

Trematode infections. *Clonorchis sinensis* or liver fluke is an important hepatic fluke of man; *Fasciola hepatica* and *Dicrocoelium lanceatum* rarely infect mankind.

Clonorchis sinensis or *distoma sinensis* lives in large numbers (several thousands) in the bile ducts and dilated biliary canals in the liver. It is widely prevalent in Eastern Asia and Indo-China. Injections of arsenicals and tartar emetic have been successful in some cases.

Oil of chenopodium is said to have some effect on clonorchis in man and animals. Emetics have been recommended, as vomiting dislodges the parasites and expels them. Tartar emetic combined with intensive courses of sulpharsenol has been recommended, the injections of the two drugs being given alternately. Mercurochrome by the mouth as well as intravenously proved ineffective. Injection of methyl violet, crystal violet and Nile blue sulphate have been tried against *Clonorchis sinensis*, but these drugs have been found ineffective. Gentian violet in doses of 15 to 20 mgm. per kilo. can be tolerated by the mouth. Intravenous injections of a 1.0 per cent. solution are said to be very effective against clonorchis; 20 c.cm. are given for the first dose followed by 30 c.cm. three days after. No untoward symptoms are observed and eggs disappear from the faeces.

Fasciola hepatica or *distomum hepaticum* is much rarer in man but common in sheep. Injections of antimony have been advised; carbon tetrachloride is useful.

Paragonimus westermani or *ringeri* occurs in Japan, Korea and China. The cercarial stage develops in snails of the genus *Melania*. It especially affects the lungs of man, producing hæmoptysis. Emetine injections are useful.

Fasciolopsis buski infects pigs and is occasionally found in man in the East Indies, Bengal, Assam and China. Thymol is mainly relied on and carbon tetrachloride is said to be more efficacious; 75 grains (5.0 gm.) of beta-naphthol in adults

divided into three doses given hourly are said to be more satisfactory.

Gastrodiscus (Amphislomum) hominis is met with in human intestines in India, Assam, Malay States and Indo-China. Its pathogenesis is doubtful. The first drug used for attacking flukes was aspidium or male fern as early as 1884. Drugs such as calomel, aloes, sodium salicylate, compounds of arsenic, mercury and antimony have been tried but the results have not been encouraging.

Blood flukes. Human schistosome infection is common in Egypt, South Africa, China and Japan. The adult worms live in the portal veins and its tributaries and lay ova which work their way to the venules on the surface of the bladder or rectum.

Schistosomes. Three species occur in human subjects. *S. japonicum* occurs in Eastern Asia especially China; *S. hæmatobium* affects the genito-urinary tract, and *S. mansoni* mainly involves the lower portion of large gut. The last-named is more widely prevalent in Africa, and to a less extent in south-west Asia and tropical America. The larval worms of *S. japonicum* after escaping from the snail, penetrate the skin of man. After infection of the definitive host, sex differentiation is recognisable by the 6th day, mating occurs by the 17th day, but sexual maturity is not attained until the 30th day. In the absence of males the female flukes remain immature for months until a male is introduced, when they mature rapidly. The intermediate host of *S. japonicum* is *Hemibia japonica* and *H. hupensis*; of *S. mansoni* is *Planorbis boissyi* in Egypt and *P. guadeloupensis* and *P. olivaceus*. *S. hæmatobium* also passes through another genus of snails (*Bullinus*), several species of which could be infected by the miracidium. In South Africa *Physopsis africana*, in Iraq *Bullinus contortus* are implicated. The adult worms may be numerous in the portal veins without causing trouble, except sometimes producing thrombosis. The main pathological lesions are caused by the very numerous spined ova irritating the tissues during their sojourn in them or during their passage through the wall of the bladder to escape in the urine in case of *S. hæmatobium* and through the rectal

mucosa in the case of *S. mansoni* and *S. japonicum*. The last two accumulate in the liver and produce severe intractable cirrhosis of the organ and ascites. The spleen may be very enlarged. Warty and papilomatous growth may occur in the genitals, resembling venereal warts or carcinoma. The presence of ova in all the abdominal organs, the lungs, heart, and cerebro-spinal system has been described; tubercle-like miliary bodies may occur in these organs. An antigen from the infected snail's liver has been prepared and a positive complement-fixation test is obtained in 88.8 per cent. of infected cases. Treatment with tartar emetic and emeline is successful. Internal administration of extract of filix mass was tried in this infection with beneficial results. Thymo-benzene (2 grains thymol in $2\frac{1}{2}$ drachm benzene) organic arsenicals, santonin and methylene blue have all been tried with unsatisfactory results. The treatment with tartar emetic has been discussed elsewhere.

Cestode infection—Tapeworm cysts. The important somatic tapeworm infections of man are cysticercosis or infection with the bladder-worms of *Tænia solium*; hydatid disease or infection with the cysts of *Echinococcus granulosus*; and sparganiasis or infection with *Sparganum*, the larval stage of *Diphyllbothrium* species. The anthelmintic treatment of these infections is not hopeful at present. Male fern, koussou, kamala and pomegranate bark have all been tried but are useless.

Nematode infections—Nemathelminthiasis. *Dracontiasis* or guinea-worm infection of the subcutaneous tissue has been known from very ancient times and they are probably the 'fiery serpents' mentioned by Moses. It is a tropical disease and occurs in Africa, Asia-Minor, Arabia and India. In India, it is practically limited to the western half. On the eastern half, it is comparatively rare or absent. The infection is fairly common in the following areas in India:—North-Western Frontier Province, the Punjab, Rajputana, Central India, Bombay, Madras and Mysore. In other parts of India such as Bengal, Assam, Bihar and Orissa, and the United Provinces the disease is unknown. The factors which determine the distribution in India are at present obscure.

The female worm which is much larger than the male is 30 to 120 cm. long and 0.5 to 1.7 mm. in diameter. When gravid it migrates to the extremities. A blister is formed at the site where the worm emerges. The embryos are usually discharged whenever the worm comes in contact with water. The pathology and transmission of the disease was studied in detail by Pedschenko in 1870 who showed that fresh-water cyclops act as intermediary host. When the embryos are swallowed by the cyclops they pass into the hæmocele cavity of the cyclops where they undergo metamorphosis. In about 4-5 weeks the larvæ become mature and are ready to enter the human host. When these infested cyclops are swallowed by man the cyclops are killed by the gastric juice, but the larvæ being more active emerge from the cyclops and enter the stomach wall. They mature in the retroperitoneal tissue in about a year. After fertilisation the male worm dies and the female migrates to the limbs, which are likely to come in contact with water.

During the period of incubation no signs or symptoms are present. Just before the worm emerges from the tissue anaphylactoid symptoms like urticaria, nausea, vomiting, giddiness, dyspnoea or fever appear. These are due to absorption of the toxin secreted by the worm. Normally it takes about three weeks for the worm to empty the uterine contents. During this period if the worm breaks, serious complications are caused, resulting in cellulitis and septicæmia which sometimes end fatally. When the worm is unable to reach the surface of the skin during the migration it dies and may produce an abscess or become calcified. This may give rise to painful joints, rheumatic pains in the limbs, etc., thus causing considerable physical disability.

Complement-fixation and dermal tests with the *Dirofilaria immitis* antigen have recently been carried out in guinea-worm infection which show in all cases positive reactions.

Treatment. A very ancient method of treatment still in vogue in endemic areas is to apply cold water to the worm, which causes the uterus to empty gradually. This process is repeated daily for two to three weeks when the worm is wound on a match-stick or a similar object. If the worm breaks during the process of winding, abscess formation or sloughing results. Recently, injections of antiseptics into the body of the worm have been recommended. This is done with the object of killing the worm, when it can be extracted easily. Injections of mercuric chloride 1 in 1000 have been recommended. Acton obtained good results by injecting chinolol 1 in 400. Recently, acriflavine 1 in 1000 has been reported to yield similar results. Macfie obtained good results in dracontiasis by

a dose of injecting tartar emetic intravenously; a dose of one grain was given every other day for 4 or 5 injections.

Prevention of guinea-worm infection is simple. Drinking-water should be boiled or filtered through a fine muslin.

FILARIASIS

The principal human somatic or extra-intestinal parasites, the filariae, are situated in lymph glands or ducts. Several varieties of filariae occur as human parasites and in some sub-tropical climates produce various clinical conditions. *Wuchereria bancrofti* is widespread in most tropical countries and occurs in many of the temperate climates. The carrier is *Culex fatigans* (also called *Culex quinquefasciatus*) but other species of mosquito may also carry it. *Loa loa* is found in West Africa. With the exception of surgical measures to remove the parasite from the eye or subcutaneous tissues, there is no treatment. *Microfilaria perstans* is found in the blood of people in the West and Central Africa. *Onchocerca volvulus* is prevalent on the Gold Coast and gives rise to localised tumours. *Microfilaria nuda* is thought to be the embryos of this and the carrier is probably *Simulium damnosum*, a day-biting fly. No treatment is known.

Filarial infection was known in India from early times. The infection is present chiefly along the sea coast and along the banks of big rivers with the exception of the Indus. The disease is caused by the filarial parasite which lives in the lymphatic vessels and glands and bring about obstruction to the lymph-flow. The embryos (microfilariae) circulate in the blood exhibiting a nocturnal periodicity. Several human filarial parasites are known of which *Wuchereria bancrofti* is the most important. The male worm is 30 to 40 mm. long and the female 70 to 80 mm.

The infection is transmitted by the mosquito. Both culicine and anophiline mosquitoes act as intermediary hosts but *Culex fatigans* is the most important carrier in India. The embryo undergoes metamorphosis in the thoracic muscles of the mosquito and under favourable conditions it takes 9 days to develop. Researches by Acton and Rao have clearly brought out the various factors that are responsible for the spread of the infection. The most important of these are, (1) optimum conditions of humidity (above 60 per cent.) and temperature (80° to 90°F.); (2) density of human population, and (3) prevalence of the carrier—*Culex fatigans*. A correlation or absence of any of these factors explains the variation in the amount of infection prevalent in different

areas. It is generally found that the infection is heaviest in towns and big villages and comparatively less in the cities, the small villages being practically free.

The clinical manifestations due to *Wuchereria bancrofti* are lymphangitis, abscess, elephantiasis of extremities, genitals and breasts, lymph varix and chyluria. Anaphylactic symptoms such as urticaria, periodical headache, and small rises in temperature, are commonly observed in infected persons. These lesions are primarily caused by the toxin of the parasite. The disease is aggravated by secondary infection. In the early stages of the infection the embryos are present in the blood but as obstruction to the lymph flow increases the embryos cease to be present in the blood. In advanced stages, the adult parasite is usually dead and becomes absorbed or calcified. In cases of chyluria, however, the lymphatics are blocked, and the blood examination reveals microfilaria. When the worm is dead, as happens in advanced cases of chyluria, no microfilaria are to be seen in the blood or urine.

A survey of the filarial disease in this country reveals certain striking features of distribution. In hyperendemic areas such as in Cochin with a microfilaria rate of above 20 per cent., the prevalent type of filarial disease is elephantiasis; lesions caused by obstruction to the juxta-aortic glands are rare. On the other hand, in areas of low endemicity (microfilaria-rate below 10 per cent.) as for example in Allahabad, the common types of lesion are lymph-varix and chyluria, elephantiasis being rare; whereas in moderately endemic areas (microfilaria-rate between 10 to 20 per cent.) one finds all types of filarial disease. It has been suggested that this variation in the type of filarial disease is due to the intensity as well as the period of infection in a locality.

For diagnosis of filarial infection, blood examination for microfilaria and eosinophilia is usually relied upon. In addition to these methods recent research has shown that it is possible to detect the presence of the infection by dermal and complement-fixation tests.

Treatment. Treatment for filarial infection may be dealt with under the following headings:—

(1) **Anaphylactoid symptoms.** The production of anaphylactic symptoms varies with individual susceptibility. Every case should be carefully investigated and treated accordingly. In addition, vaccines made from the various strains of streptococci and staphylococci and arsenical compounds such as soamin have been found to give the best results in the treatment of anaphylactoid signs and symptoms.

• (2) **Filarial disease.** Lymphangitis, abscess and elephantiasis are the common manifestations of filarial infection.

In a large number of cases the acute attacks are due to secondary infection. When they are caused by streptococci high temperature sets in with a fairly high leucocyte count. When the infection is in the spermatic cord it tends to spread towards the peritoneum and sometimes proves fatal. Staphylococcal infection shows milder reaction—the fever is 101° to 102°F. and leucocytosis is not so high. Pus is often formed with formation of abscess. For acute signs and symptoms, the treatment is symptomatic and consists of rest, ice application, diaphoretics, and local application of sedative lotions like calamine, polyvalent streptococcal sera may also be given. In case of abscess formation surgical treatment is necessary.

In cases of elephantiasis surgical operation for excision of hypertrophied tissue has been recommended. It should be remembered, however, that such operations will not cure the disease. Massage, pressure bandages, prevention of secondary infection and treatment for the same are helpful in reducing the size of the limb and checking its growth. Periodical courses of mixed streptococcal and staphylococcal vaccines have been found to give the best results. In case of genital affection, surgical treatment for the excision of elephantoid tissue is recommended.

Lymph varix. In the early stages application of suspensory or pressure bandages together with treatment for filarial infection is recommended. In advanced cases surgical operation for removal of varix may be necessary.

A large amount of work has been carried out in searching for specific drug for filarial infection, but no success has been attained so far. Many drugs, chiefly compounds of arsenic, antimony, bismuth and copper have been tried without success. Investigations have been carried out with compounds of zinc, lead, tin and gold. Various synthetic and vegetable alkaloids have been tried orally and also by injection, but no success has attended any of these experiments.

Prophylaxis of filarial infection consists chiefly in anti-mosquito measures and isolation of the early infected cases (carriers).

Chyluria, lymphuria or hæmato-chyluria. Blockage by *Wuchereria bancrofti* at the level of (1) the juxta-aortic

glands which drain the lymphatics of the kidneys, or (2) the iliac (internal) glands which drain the lymphatics of the bladder, results in lymph-varix which ruptures on strain or trauma, and leads to leakage of chyle or lymph sometimes mixed with blood. The urine is clear in the morning or after rest but becomes milky after a fatty meal. Cystoscopic and pyelographic examinations are helpful in locating the site and the side affected. Secondary infection is very common in chyluria—culture of a catheter specimen or midstream urine shows streptococci or staphylococci.

Microfilariae are always present in the blood and in urine in cases of chyluria. They are absent in long-standing cases when the parasites are dead. Sometimes they are present only in blood or only in the urine.

Complement-fixation test with the *Dirofilaria immitis* antigen is positive in cases of chyluria. Dermal tests with the same antigen have given negative results so far. Chyluria cases show a constant moderate eosinophilia (above 5 per cent.).

For the treatment of these conditions absolute rest is necessary. Restriction of fats and fluids is essential. The focus or foci should be eradicated, secondary infection treated with autovaccine or stock vaccines (streptococci and staphylococci albus and aureus). Salol, methylene blue, urotropine, picric acid, quinine and potassium iodide have been tried but do not seem to have any specific effect. Astringent injections of Ext. hamamelis liq. or tannic or gallic acid into the bladder give relief. The cautery is helpful in closing the leak in the bladder. Sodium citrate in large doses is given to prevent clotting of chyle in the bladder. The following have been tried with beneficial results:—

Arsenic compounds.

Soamin, subcutaneously, intramuscularly or intravenously; commence with 1 gr. (0.06 gm.) to maximum 3 gr. (0.2 gm.), twice weekly. Total 20-25 gr. (1.3 to 1.6 gm.).

N.A.B., neosalvarsan or sulfarsenol, 4-6 doses.

Tryparsamide, 2 gm. in 10 c.cm. of distilled water intravenously once a week, not exceeding a total of 8 gm.

Antimony compounds.

S.A.T. 2 per cent. solution intravenously commencing with 1 c.cm. and gradually increase to 5 c.cm. twice a week. Total of 2.5 to 3 gm.

Fouadin, 1.5 c.cm., 3 c.cm. and 5 c.cm. intramuscularly or intravenously daily. Total 30 to 40 c.cm.

Urea-stibamine, stiburea or aminostiburea 0.1 gm. to 0.3 gm. in distilled water intravenously twice a week. Total 2.5 to 3 gm.

Neostibosan, 0.1 to 0.3 gm. in distilled water intravenously, daily. Total 3 gm.

ANTIMONY COMPOUNDS

Schistosomiasis. Bilharziasis has been successfully treated by injections of tartar emetic. It was at one time thought that there was no means of destroying these parasites but MacDonagh (1915) first recommended and Christopherson (1918) first tried, and showed that injections of the double salts of antimony are successful in eradicating both kinds of African schistosome infection—*S. haematobium* and *S. mansoni*. Tyau (1922) and Tootall (1923) showed the efficacy of antimony injections against the related parasite *S. japonicum*. The routine followed by Christopherson is to begin with $\frac{1}{4}$ grain (0.015 gm.) doses for children and $\frac{1}{2}$ grain (0.03 gm.) for adults, dissolved in 20 min. of distilled water and then diluted with an equal quantity of normal saline. The dose is increased by half a grain up to $2\frac{1}{4}$ grains (0.1 gm.) unless a reaction is produced before that time. Injections are given every other day, the dosage being kept between 2 to $2\frac{1}{4}$ grains (0.13 to 0.16 gm.) until 25 to 30 grains (1.7 to 2.0 gm.) have been given. This amount is usually sufficient to cure an adult; children are given proportionately smaller doses, the maximum dose being on the basis of 0.003 gm. (3 mgm.) per kilo. body weight. In out-patient clinics in Egypt over a 100,000 patients are treated annually, the treatment used being a course of 12 injections, given three times a week, and totalling 22.5 grains (1.5 gm.) of tartar emetic; this cures 80 to 97 per cent.

of cases. The effects of the treatment are most striking. After a few injections the vesical pain and the scalding sensation disappear. Blood is also absent from the urine though sometimes it may persist a little longer. After the full course the urine becomes clear and normal in colour; this change probably corresponds with the cessation of the activities of the parasites and the cure of the disease. This course is suitable for the early stage of the disease when the patient is in a good state of health. In old-standing cases, where they are weak and emaciated, a less intensive course is desirable. A slight coughing at the end of the injection is not a contra-indication for continuing the treatment, but if nausea, vomiting, abdominal pains, giddiness and diarrhoea supervene the patient should be given a few days rest. If more than 25 grains are required it is better to give a second course after an interval of a fortnight or more. Lampe (1926) gave to out-patients 150 to 250 c.cm. of a 1.0 per cent. solution in 6 to 7 weeks, to in-patients, a more intensive course of 200 to 240 c.cm. in 4 to 5 weeks was given. As a rule no untoward symptoms occurred. Lampe's conclusions are in accord with those of Christopherson and he considers 25 to 30 grains (1.6 to 2 gm.) spread over 6 to 7 weeks the best treatment. It is best to continue treatment for a week or 10 days after all ova and leucocytes have disappeared from the urine after centrifugalising.

Usually after the injections have been given for a week or 10 days, improvement begins." In *S. hæmatobium* the vesical pains disappear, the urine clears up, and so does the scalding sensation when the urine is passed. In the case of *S. mansoni* and *S. japonicum* the blood in the fæces decreases, fever disappears gradually and the asthenia and malaise improve. In favourable cases eggs may disappear in 10-15 days. In severe cases dead ova are passed intermittently for weeks and months after the parent worms are dead. Degeneration of miracidia is seen early, generally after about 12 grains have been given. The ova become shrunken, shrivelled and blackish and later do not hatch out in water. When this stage is attained the parent worm is killed and the ova are sterilised *in situ*. As a rule 30 grains (2.0 gm.) of the tartrate administered

in from 28-30 days form the curative dose. The rapidity and permanence of cure, according to Khalil (1924) are less dependent on the total amount of antimony administered than on a regular tri-weekly series of injections. Re-examinations of patients who have been given a course of 12 injections show that 80 per cent. to 97 per cent. are cured completely.

Mode of action. The drug kills not only the adult worms but penetrates the shells and kills the ova deposited in the tissues. This can be demonstrated by adding tartar emetic to 6 c.cm. of warm water at 133°F. to which a little urine containing ova has been added. It is found that if the antimony salt is not added, the ova begin to hatch out in 4 to 5 minutes and that most of them have hatched out in an hour. If, however, a grain of tartar emetic is added to the water only half the ova hatch out and a good many are found to be dead, half in and half out of the shell. If the concentration is further increased very few embryos hatch out and even the few found swimming do not survive long. Under the microscope one can watch the darting, pulsating, corkscrew movements of the miracidia slowing down in contact with tartar emetic solution. Microscopic examination of eggs voided during injections of antimony show that they have undergone degeneration. It is a curious fact that pentavalent antimony derivatives have no effect in bilharziasis. Hamilton Fairley (1924) showed that the lethal effect of tartar emetic *in vitro* was greatly enhanced in the presence of human serum. Everything points to the fact that tartar emetic is a powerful therapeutic agent in the treatment of all schistosome infections. Even in patients undergoing surgical treatment a course of antimony is desirable.

Relapses. Hamilton Fairley (1924) was of opinion that tartar emetic, in a proportion of cases, merely reduced the parasitic level and converted cases of frank clinical schistosomiasis into passive carriers in whom ova are shed in small quantity and at such irregular intervals as to escape detection on one or more isolated examinations. He tried the drug in *S. spindalis* in goats and got results which suggested that the antimonyl tartrates were less effective than emetine. These results, however, cannot be applied to the human disease and

investigations in Egypt show that emetine is not as effective as tartar emetic. Day (1924) showed that comparatively small doses of antimony (25 grains of tartar emetic) are required to kill the ova present in the tissues, and that reappearance of ova in the urine after small doses, is due to the fact that a sufficient quantity of the antimony salt has been given to kill the ova but not the adult parasites, which have only been temporarily affected by these small doses. Relapses are due to lack of judgment with regard to dosage; if a sufficient quantity of antimony compounds are given no relapses occur. It has been shown that 20 per cent. of cases relapse after 2 years with 0.7 gm., 15 per cent. have viable ova after 1.3 gm.; after a full course of 2 gm. 3.5 per cent. still remain infected. The usual cure rate is 79 per cent. In uncomplicated cases, as a rule, 25 grains (1.6 gm.) produce a complete cure, but the total quantity of the drug varies largely in different individuals and every case should be treated on its own merits. Even in the worst cases the mortality is reduced to half.

Antimony tartrates thus have a strong parasito-tropic action on all forms of human schistosomiasis, but their action on other helminths, even on other trematodes, needs further investigation.

During recent years carbon tetrachloride has been suggested as an adjuvant to treatment with tartar emetic. It is said that after one or more doses of carbon tetrachloride the adult worms show signs of degeneration and it is hoped that massive doses of the drug at long interval, to enable the system to recover from its effect, may eradicate the disease. The following preparations of antimony, in addition to tartar emetic, have been used in schistosomiasis.

Bayer SB 212 is a complex salt of organic antimonyl acid containing 25 per cent. of antimony. It can be given intramuscularly, the site of injection being frequently changed.

Antimosan (Von Heyden 461) is said to be effective against *S. japonicum* but it is expensive. It can be given intramuscularly and intravenously. Its efficacy is doubtful.

Fouadin or neo-antimosan. It is a trivalent compound of antimony containing 0.0055 gm. of antimony in 1.0 c.cm. and it is a pyrocatechin sodium disulphonate compound. It has given good results in schistoso-

miasis; 3.0 c.cm. of the drug are given intramuscularly (in gluteal region). Antimosan is said to be well tolerated. Seven per cent. solution is stable. Course recommended:—first day 1.5 c.cm., second day 3.5 c.cm., third day 5.0 c.cm., and then on alternate days till the fifteenth day to a total of 40 c.cm.

Filariasis. Recent observation in human filariasis shows that antimony compounds have no marked effect upon the embryos in the blood though some observers have thought that the number of embryos in the blood shows a marked decrease. Prolonged trials of the antimonyl tartrates in this disease show that the drug has no effect on the adult parasites. Chopra and Sunder Rao (1929) tried almost all the pentavalent organic compounds of antimony, *e.g.*, urea-stibamine, stibosan, neo-stibosan, etc., in filariasis without any effect. The same is the case with other helminthic infestations, *e.g.*, lung infections (paragonimiasis).

Guinea-worm infection is said to be beneficially affected by intravenous injections of tartar emetic. The worm and the embryos are killed, the inflammation is relieved and as a rule a total of six grains of tartar emetic is said to suffice to clear the infection, though in some cases a longer course has to be given. Sometimes, the injections have the effect of bringing to the surface other guinea-worms, which happen to be in the body. Macfie (1922) treated 23 cases of guinea-worm infection with tartar emetic intravenously giving 1 grain (0.06 gm.) every other day. The drug gave encouraging results in this series but was not infallible. In 14 cases complete expulsion of the worms occurred after 4 or 5 injections; in 10 cases, although the worms were not expelled the inflammatory phenomena in connection with it disappeared. Hamilton Fairley tried antimony tartrates in guinea-worm infections without success, he prefers emetine injections given intravenously.

Trichinosis. Injections of tartar emetic relieve symptoms such as fever and muscular pains. Grove (1925) successfully treated a case but further trials are recommended.

Flukes. Antimonyl tartrates have been tried in the treatment of infection with flukes but the results so far have not been satisfactory. The method of administration and dosage are the same as those used in kala-azar.

EMETINE AND OTHER DRUGS

Schistosomiasis. Although emetine hydrochloride does not kill the bilharzial cercariæ (*S. spindalis*) *in vitro* in 1 in 100 dilutions, in the presence of serum it kills them in dilutions of 1 in 160,000. The lethal effects of both emetine and tartar emetic are greatly enhanced in the presence of human serum.

Intravenous and intramuscular injections of emetine have been used in the treatment of *Bilharzia hæmatobium* by many authorities, and have succeeded in permanently eradicating the infection. Six daily injections of 1 grain (0.06 gm.) each are given, followed by an intermission of six days, when a second series of 6 injections is given. In children doses of $\frac{1}{4}$ gr (0.032 gm.) are often sufficient. No living parasites or ova can be found after the fifteenth injection. Emetine is specially indicated in patients who are intolerant to antimony. The drug acts on the ova which show degenerative changes; it also kills the adult worms gradually. Diamantis (1918; 1921) reported a number of cases of *S. hæmatobium* infection which were cured by emetine injections. He gave the drug intravenously in doses of 0.12 gm., 10 to 12 injections at intervals of 3 to 5 days; 0.8 to 1.05 gm. of emetine in all, produced a cure. It is also effective against *S. mansoni*. In urinary schistosomiasis the length of treatment and dosage are both important. Harkness (1920) gave a total of 14 grains (1.0 gm.) and a further total of 20 gr. without effecting a cure. Cawston (1922) recommended emetine dissolved in 20 minims of a 1 per cent. solution of carbolic acid, intramuscularly for 8 consecutive days and then thrice weekly for three weeks. Cardiac depression occurs in the second and third week but it can be avoided by giving digitalis. He gives emetine in preference to antimonyl tartrates in children and young people in whom it is difficult to get into veins. According to him curative doses of emetine for schistosomiasis is double that given for amoebic dysentery. *S. japonicum* has been cured with emetine injections starting with $\frac{1}{4}$ grain and increasing the dose to 2 grains daily, as toleration developed; two courses of 15 grains each with an interval of one week are recommended. Cawston (1926) held that unless very large doses of emetine are given uninterruptedly emetine cannot be depended on in schistosomiasis. Such doses are very risky and are not to be recommended. Emetine periodide has been recommended in the treatment of *S. hæmatobium* in doses of 1 grain (0.06 gm.) three times a day. The drug does not produce any toxic symptoms and appears to have curative properties. Auremetine given intravenously is also said to be effective.

It will be seen from the above review of the literature that emetine should only be used in those cases of schistosomiasis which are intolerant to antimonyl tartrates or in children in whom it is difficult to find the veins. In cases of intestinal schistosomiasis complicated by amoebic dysentery, emetine is indicated. Its dosage should be carefully regulated and if toxic symptoms appear it should not be continued.

Emetine in other helminthic infestations. Emetine has been found useful in infestations of the liver with *Fasciola hepatica* and *F. gigantica*. Kikilko and Imamura (1920) found daily injections of emetine useful in clonorchis infections.

Emetine injections have been recommended in the treatment of dracontiasis. Tournier (1923) treated 17 cases of this infection by giving emetine intravenously and by the mouth, with good results. This has not however been confirmed by other observers. Emetine in daily injections is said to be valuable in ameliorating symptoms produced in paragonimiasis, but these cases need careful watching for the onset of toxic symptoms. Potassium iodide and tartar emetic injections are preferable.

Emetine preparations have been tried against filarial infections, especially of *W. bancrofti*, but without effect.

Organic arsenicals in helminthic infestations. Some of the organic compounds of arsenic have been tried against intestinal parasites as well as in somatic infections. Given by the mouth stovarsol is said to have a vermifugal action. A 10 per cent. solution of stovarsol has no effect on ascaris *in vitro* but when mixed with intestinal juices it becomes active. Injections of salvarsan have been used against clonorchis. Intravenously, organic arsenicals have been tried against oxyuris as well as guinea worm infections; against intestinal and blood flukes they have been tried without success. Neosalvarsan has been tried in hydatid disease in man without success. Experiments on rabbits show that hydatid material given with salvarsan does not prevent cyst formation.

Aniline dyes in helminthic infestations. The use of aniline dyes as anthelmintics is yet in its infancy. Methylene blue has

been tried against clonorchis in Japan with some degree of success. *In vitro* experiments show that living flukes are susceptible to methyl violet, crystal violet and Nile blue sulphate. Methyl violet given intravenously to dogs stains the liver intensely and is excreted in the bile, but concentrations fatal to the worms are very toxic to the host; Nile blue is even more toxic. Mercurochrome 220 (hydroxymercuric dibromofluorescein) and gentian violet have also been tried in clonorchiasis. The certified gentian violet (either penta-methyl or hexamethyl pararosaniline or else a mixture of the two compounds) is definitely toxic to the worms, and after doses of 50 mgm. per kilo. of body weight, by the mouth, produces a definite decrease in the egg count; smaller doses such as 16 mgm. per kilo. are less effective. With 50 mgm. per kilo., however, symptoms of intoxication characterised by vomiting and loss of weight are produced; 35 mgm. per kilo. produce no toxic effects, but in heavy infections where there is much damage of the liver, 15 to 17 mgm. per kilo. is a suitable dose. In man the results are not so good. Twenty c.cm. of a 1 per cent. solution of gentian violet given intravenously, followed 3 days later by 30 c.cm. caused the disappearance of ova in one case.

Among other dyes, malachite green, brilliant green, crystal violet, fuchsine, Congo red, trypan red, trypan blue and thionin blue have been tried. Both acid and alkaline dyes showed some toxicity on the cysticercus and on the larvæ, but no experiments have been carried out *in vivo*.

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PART III

REMEDIES USED AGAINST PROTOZOAL DISEASES

The commonest diseases which are caused by protozoal organisms in tropical climates may be grouped as follows :—

- (1) Amoebiasis (dysentery, etc.).
- (2) Leishmaniasis (kala-azar).
- (3) Trypanosomiasis (sleeping sickness).
- (4) Haemosporidia infections (malaria and blackwater fever).

From very early times, attempts have been made to influence these diseases by drugs. Countless drugs have been introduced empirically from time to time for the treatment of parasitic diseases only to be discarded after more prolonged trials. The work of Ehrlich opened up a new field for the scientific assessment of the value of drugs. During the years that followed, rapid advances were made in this field of chemotherapeutic research. Helminths, protozoa and spirochaetes can be readily detected by direct examination by the microscope and hence the influence of drugs on these organisms has been studied in an elaborate fashion. Though the mode of action of these drugs has not been clearly explained, certain interesting data have been obtained which are worth recording. Emetine and its derivatives and the cinchona alkaloids have been found to act on some protozoal organisms, while compounds of arsenic, antimony and bismuth have a well-marked toxic action on others. Compounds of mercury as well as aniline dyes show a marked activity against some protozoa, but these have the limitation of being also toxic to the host.

The recognition of trypanosoma infections in experimental animals and their behaviour under the influence of drugs injected or administered otherwise, has made it possible for the scientists to study the mode of action of various remedies under laboratory

conditions. Kolmer has studied the trypanocidal activity of certain remedies on *T. equiperdum* and has shown that different drugs have different degrees of toxicity to this organism.

Name of compounds.	Motility 15 minutes.		Rat inoculation tests.		Results.
	Present.	Absent.	Dilution.		
Trypan red ...	1 in 20,000	1 in 10,000	1 in 10,000	+	
Atoxyl ...		1 in 200	1 in 200	-	
Tryparsamide ...		1 in 200	1 in 200	-	
Salvarsan & Neo-salvarsan ...	1 in 320,000	1 in 160,000	1 in 160,000	-	
Mercuric chloride	1 in 5,000,000	1 in 250,000	+	
Tartar emetic	1 in 10,000,000	1 in 5,000,000	+	
Tartro-bismuthate of sodium & potassium. ...	1 in 200	1 in 100	1 in 100	-	

It will be seen that tartar emetic is strongly trypanocidal *in vitro*, then follow mercury and arsenic preparations. The pentavalent compounds of arsenic are much less active, and bismuth compounds and the aniline dyes are still less. In many instances, in dilutions sufficient to destroy motility, they are trypanocidal in animals, but this is not so in the case of tartar emetic. Loss of motility, however, does not always mean death. In a general way, it may be said that there is relationship between activity *in vitro* and *in vivo*, though of course there are many exceptions. The activity of trivalent organic arsenicals is very high *in vivo* and *in vitro*.

During the last few years, certain definite advances have been made in the chemotherapeutic treatment of protozoal diseases and in the following chapters the present position of our knowledge regarding these drugs will be presented.

Classification of Drugs Acting on Protozoal Infections

(1) *Amoebiasis* and intestinal flagellate infections. Ipecacuanha and its derivatives, *Holarrhena antidysenterica* and its derivatives, yatren, stovarsol, carbarsone, etc. Such drugs as *Plantago ovata* (Isabgul), and *Ægle marmelos* (Bael fruit) have only palliative action.

(2) **Leishmaniasis.** Antimony compounds, Arsenicals, Bayer 205.

(3) **Trypanosomiasis.** Arsenicals; Bayer 205 and Fournieu 309 (Moranyl); antimonials, bismuth compounds, quinoline derivatives.

(4) **Hæmosporidial infections (Malaria).** Cinchona alkaloids, plasmochin, atebirin, malarcan, tebetren.

VACCINE THERAPY IN PROTOZOAL DISEASES

During recent years evidence has been brought forward to show that immunity may develop in protozoal diseases, and in accordance with this hypothesis vaccines have been tried by several workers in the treatment of protozoal infections. It must be pointed out, however, that in contradistinction to bacterial diseases, the phenomenon of immunity in protozoal infections generally is still problematical and vaccine therapy in the latter group is yet in experimental stage.

For the rational and successful employment of vaccine therapy in infectious diseases in general, three conditions need to be satisfied: (1) The ætiological agent of the disease should be one that can be isolated and grown in a form suitable for the manufacture of vaccine; (2) the mechanism of cure of the disease should be one in which the natural processes of defence such as the antibody and the phagocytic mechanisms play an important part; (3) the treatment of the disease with drugs should be in an unsatisfactory state and sufficient experimental evidence present to indicate that vaccine therapy will be beneficial when employed alone or in combination with drug therapy. Applying these three criteria to vaccine therapy in protozoal diseases we find that there is very little need or justification at present for the employment of this therapy in human beings except in a few conditions in which specific drugs of value have not yet been discovered. The following is a brief outline of the evidence on which the above conclusion is based.

Judged from the point of view of the first criterion mentioned above we find that there are many technical difficulties in the way of preparing suitable vaccines out of most of the pathogenic protozoa that infect man. Protozoal organisms compared to

bacteria, are rather difficult to grow *in vitro* in artificial culture media and the only protozoa that have so far been successfully cultivated on a large scale and in a form suitable for vaccine production are *Leishmania tropica*, *Leishmania donovani*, and *Entamoeba histolytica*. Others such as the trypanosomes plasmodia, etc., are not only difficult to grow outside the body but it is also not easy to obtain them in a pure state for vaccine manufacture. The types of protozoal vaccine that have commonly been employed in experimental work on laboratory animals are (a) attenuated living organisms, (b) virulent organisms which after inoculation are controlled by treatment and (c) dead or disintegrated organisms and their products. For use in human beings the first two are unsuited and the third which may prove useful is not available in all cases.

Judged from the point of view of the second criterion, vaccine therapy does not appear to be any more satisfactory. The chief object in injecting vaccines being the elaboration of antibodies for the purpose of destroying the infecting agent, we would naturally wish to ascertain, before employing it, whether (a) there is sufficient evidence to prove that antibodies are formed in protozoal infections, and (b) if so, whether these antibodies play any important part in overcoming these infections. Although our knowledge of the immunity mechanism in protozoal infections is very imperfect, there is some evidence that antibodies are formed in certain protozoal diseases particularly those due to the hæmoprotezoa; but in these diseases there is no certainty that the antibodies elaborated are of real value in immunity. In trypanosomiasis and leishmaniasis, the lytic, opsonic and anti-reproductive antibodies that are formed are supposed to play a part in the overcoming of these infections; but, both on account of the complexity and variability of the antigens present in these organisms as well as due to their possessing powers of adaptation and resistance against the injurious action of antibodies it is not possible to assess correctly the value of antibodies in immunity to protozoal diseases. Furthermore there is evidence to suggest that in other protozoal infections as for example the plasmodium infections, immunity is dependent upon the sensitiveness of the phagocytic mechanism

and also upon certain non-specific factors such as alterations in cell permeability, variations in bio-chemical conditions and in the nature of available food supply. If it is so then it is still more difficult to say how far the use of specific antigens (vaccines) and the presence of specific antibodies can be of benefit in overcoming these infections.

Judged from the third and last criterion, we find again that vaccine therapy in protozoal diseases can at best be only of limited value. The treatment of most of these diseases with drugs is in quite a satisfactory state and there is little need for resorting to vaccines to bring about a cure. In malaria visceral leishmaniasis, amebiasis and trypanosomiasis specific drugs of proved merit are readily available and no practitioner would ever dream of employing vaccines in preference to them.

Taking the evidence discussed above as a whole, the manufacture and use of vaccines so far as the treatment of most protozoal diseases is concerned, may justifiably be said to be a matter of pure research or academic interest. The results of practical employment of vaccines in the different protozoal diseases recorded below further substantiate this view.

Oriental sore. It was noticed long ago that recovery from an attack of oriental sore conferred immunity to a second attack. This observation was put to practical use and individuals were inoculated with material from a sore on certain unexposed surface of the body in the hope that after recovery from the attack of the disease, immunity would be produced and lesions on the face, etc., would not occur and cause disfigurement. The next step to this way was to prepare vaccines from cultures of the organism and try them for prophylactic purposes. Although the results were not encouraging it was realised that immunity developed only when an experimental sore was produced and was allowed to run a natural course. Row (1912) tried the effect of vaccines in the treatment of cases of oriental sore and claimed that he obtained favourable results. Ray employed a vaccine prepared in a different way to Row's (organisms were grown on solid media and killed by freezing and thawing) and claimed that it possessed remarkable curative properties. His claim has not yet been corroborated by others and the matter may be considered to be still in the experimental stage. An extensive use of the vaccine in a well controlled series of cases can alone help in elucidating its real value.

Kala-Azar. Nicolle and others found that recovery from one attack of kala-azar protected dogs and monkeys from another attack. This

led to attempts to treat kala-azar with vaccine and the results obtained by the workers were very unsatisfactory. Longo, Di Cristina and Caronia used vaccines on human cases of kala-azar and obtained very disappointing results. Napier and his co-workers (1932) used a leishmania vaccine supplied by Ray in four cases of kala-azar but the results obtained were not very encouraging. From the theoretical point of view the employment of a vaccine for the treatment of kala-azar does not appear to be either sound or justifiable. There is no evidence that in kala-azar there is a dearth of antibody due to a dearth of antigen.

Dermal leishmaniasis. A vaccine has been employed in this condition but the results have been very variable. While in a certain number of selected cases a small degree of temporary improvement was noticed, in the majority of unselected cases little benefit was obtained. Remedies such as urea stibamine and neostibosan have so far yielded decidedly better results than vaccines. Therefore the latter is worth a trial only when these drugs have failed. At the present stage it is difficult to form a correct estimate of the value of vaccine therapy in this disease; it can neither be condemned as useless nor commended as being very useful.

Trypanosomiasis. The usefulness of vaccine in this disease has been tested only in laboratory animals. Trypanosomes, which have been killed, lysed, dried or attenuated have all been employed but the results obtained are not quite satisfactory. Serological tests conducted after the administration of vaccines have revealed specific changes in the blood serum and complement fixation tests have yielded positive results. From this alone we cannot be certain whether the antibodies present are helpful in protecting the animal from subsequent infections or not. In human cases of trypanosome infections vaccines have not been tried.

Plasmodium infections. In the case of plasmodial infections of birds it has been shown that inoculations into canaries of sporozoites, which have been rendered non-infective by keeping them for 12 to 48 hours after removal from mosquitoes, rendered them immune to inoculation with virulent parasites. In human beings on the other hand the immunity to re-inoculation that develops in the course of malarial therapy of G. P. I. cases, does protect these individuals from infection when sporozoites from mosquitoes are injected.

Piroplasmosis. Vaccination with the living organism followed by treatment with specific drugs has been remarkably successful in prophylaxis.

Babesia infections. Using a vaccine made from macerated spleen and lymphatic glands of animals infected with babesia it has been shown that about 50 per cent. of the animals develop immunity and are resistant to re-inoculation. Vaccines have not been used for curative purposes in this disease.

Conclusion. From the above discussion it will be evident that the use of protozoal vaccines has so far yielded very interesting results from an immunological point of view in laboratory animals but their employment in man as a therapeutic agent has furnished neither successful nor encouraging results. It may be possible that with improvements in the technique of preparation, standardisation and administration of protozoal vaccines we may obtain in future more encouraging and beneficial results; but at the present time their value seems to be very limited, only being helpful in a few selected cases in certain special conditions. The stage is not reached in which one can safely recommend these vaccines as valuable therapeutic agents for the routine use of the general practitioner. They may, however, be used for experimental purposes by specialists in select individual cases.

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SECTION I

REMEDIES USED AGAINST AMŒBIASIS

CHAPTER I

GENERAL CONSIDERATION

Incidence of amœbiasis. Amœbic dysentery is common in India. A routine examination of the stools of patients admitted into the Carmichael Hospital for Tropical Diseases showed an incidence of 12 per cent. of infections with *E. histolytica*. According to Knowles (1928) chronic intestinal amœbiasis, as a cause of sickness and invaliding in this country, is of great importance especially among the European community. An acute attack of amœbic dysentery can, in the majority of cases, be successfully relieved by proper treatment, but eradication of the chronic intestinal infection with *E. histolytica* is a difficult matter. Although there are a number of supposed cures for amœbiasis, it may be said that *therapia magna sterilisans* has not yet been found. Most of these remedies reduce the infection to a low level so that the patients' natural powers of resistance can keep in check the parasites which still remain in the body.

The causative organism. A number of amœbæ infest man and animals but they do not all produce disease. All authorities now consider that *E. histolytica* is the pathogenic organism. The pathogenicity of *Entamœba histolytica* and the harmlessness of *E. coli* in man were shown by Walker and Sellards in 1913. The two organisms look very much alike, but they can be distinguished by the fact that in the protoplasm of *E. histolytica* numerous red corpuscles are present while *E. coli* contains bacteria and other foreign bodies. The cystic stage of the parasitic organism has a thin wall and usually contains four nuclei which can be stained with double strength iodine solution, while fully developed *E. coli* cysts have eight nuclei. The cysts appear in the stool when the acute dysenteric symptoms have subsided and they constitute the resistant stage. The cysts can live outside the body for some days and they cause new infections when swallowed with food. Experiments show that the cysts do not develop in the small intestine but in the upper part of the large where plenty of fluid is present. Dobell (1928)

described the process of excystation with the escape of a single quadrinucleate amoebæ through a minute perforation in the cyst wall. No sexual phenomena have been observed during the metacystic stage. The resistant cysts are the source of new infection which are carried by the housefly or by other means. Most cyst carriers are not healthy and require active treatment to rid them of their infection.

E. histolytica can now be cultured without difficulty on a medium containing human serum, dextrose, NaCl, KCl and NaHCO₃. The culture from stools is of practical value in establishing the presence of the organism when microscopical examinations have failed. Hæmolytic, cytolytic and complement-binding substances have been obtained from the cultures by extraction with alcohol and a complement-fixation test for the diagnosis of *E. histolytica* infections has been worked out.

Non-pathogenic entamoebæ occur in the human intestine. *E. coli* is by far the commonest organism. *Endolimax nana* resembles a small *E. coli*; its oval cyst contains four nuclei. *Iodamoeba butschlii* has a vesicular nucleus and its cysts have a signet-ring-like nucleus with a large and very prominent glycogen vacuole. *Dientamoeba fragilis* shows two nuclei. *E. dispar* can only be differentiated from *E. histolytica* by injection into the rectum of kittens.

Diagnosis. Diagnosis can be made in 75 per cent. of cases by single examination of the stool and in 90 per cent. by two examinations; as many as six examinations may, however, be necessary.

The problem of cure. Dysentery is a clinical syndrome meaning the passage of blood, pus and mucus with the stool accompanied by tenesmus, and the term has been loosely used even to cover the carriers where these symptoms are absent. Some use the word 'cure' in the sense that vegetative and cystic entamoebæ are absent while others use it to mean that the clinical symptoms have abated. The effects of treatment can only be accurately gauged by a careful examination of the stool for the presence of *E. histolytica*; for in amoebiasis a temporary or clinical cure and permanent freedom from infection are unfortunately by no means always synonymous. Some authorities take cure to mean freedom from all symptoms and absence of amoebæ in the stools for at least six months from the cessation of symptoms. This is a difficult test to be of any practical value. In the Military Hospitals during the great war the test for cure officially laid down was six negative examinations during the three weeks following the treatment, the last three examinations being done in the third week. In the Carmichael Hospital for Tropical Diseases six negative examinations on six days after the cessation of treatment are taken as the criterion of cure and for all practical purposes this suffices; moreover, when the patients are relieved of all their symptoms they cannot be persuaded to stay in the hospital much longer. The treated cases are divided into three main groups.

(1) **Failure of treatment.** If either vegetative or cystic forms of *E. histolytica* are present, the treatment has failed.

(2) **Probable cures.** If the examination of six stools after cessation of treatment gives negative results the case is probably cured. These cases however cannot be said to be absolutely cured, but the chances are on the side of a favourable prognosis.

(3) **Indeterminate cases.** If however six stools have not been obtained the case is 'indeterminate,' and the majority of cases unfortunately fall under this head in actual practice.

Latent infection and 'carriers'. The degree of severity of symptoms in an individual infected with *E. histolytica* varies widely. These variations are due to (1) variation in the resistance of different individuals to the inroads of the parasites and (2) variations in the tissue-attacking and tissue-dissolving power of different strains of the parasites. It has been shown that *E. histolytica* is not always a tissue parasite; it can occur in the large intestine without tissue penetration. A latent infection does not always mean ulceration of the bowel, but an ulcerative process may be established at any time. In latent carriers the entamoebæ live in the lumen of the gut and feed on the bacteria present there. They never invade the tissues and produce very mild symptoms. These cases are amenable to treatment.

When actual symptoms of dysentery are present, the amoebæ are numerous and in full activity, they are amenable to the action of emetine. The reason is that the gut in these conditions is hyperæmic and emetine circulating in the blood will have ready access to the amoebæ. The cases most resistant to treatment are the indeterminate group which get relapse after relapse and fail to react to any drug. In these patients there is superficial ulceration or even considerable thickening and fibrosis of the gut, the amoebæ are walled in and it becomes difficult for emetine to reach them. When there is a co-existing infection with bacillary dysentery, especially of the Flexner group, the contents of the gut are very acid and there emetine is not so effective.

Why it is that entamoebæ cause symptoms in one individual and not in another is difficult to explain. The influence of environment on the vegetative forms of *E. histolytica* is an important factor; the stasis of the gut contents and their consistency have a bearing on the encystation of the amoebæ. It is

possible that these factors play a part in the carrier problem and prevent emetine from producing its usual effect

Whenever possible, examination of the ulcer with the sigmoidoscope should be done for diagnosis as well as to see the curative effect of the drug. This instrument is of great practical use in the diagnosis of the latent stages of amœbic dysentery. Ulceration may be present without producing any pain. A healed scar after treatment is a sign that the amœbic activity has disappeared, but when traces of lesions are seen in the small depressions or pits which stud the mucosa, the disease has not been eradicated.

Diet in amœbiasis. The diet is of great importance in the early stages of treatment of acute dysentery. Less food means more rest for the inflamed intestine, but this should not be done at the expense of the patient's strength. For the first few days it is preferable to give fluid diet such as chicken broth, rice water, egg albumin or barley water. Later, milk diluted with lime water and barley water or citrated milk may be given if curds are being formed. When this is well borne pure milk or Horlick's milk or Benger's food may be substituted. Some patients, however, develop a distaste for milk and cannot digest it and such things as rice water (kanji) may be given.

Such strict dietary is not necessary for sub-acute and chronic cases. It is not necessary to restrict the diet of carriers during treatment, but such articles of diet as are irritating or leave a large residue, *e.g.*, vegetables, hot curries, etc., should be forbidden. It is advisable to stop all alcohol and also smoking during the treatment. After the completion of treatment the diet should be gradually increased, milk, puddings of sago, arrowroot, rice, cornflower, custard, etc., being given in place of milk; later lightly boiled eggs and toast or a little soft-boiled rice; fish and white meat should be added gradually.

In addition to diet restrictions, the patient should avoid chill and exposures. The patients who have suffered from amœbic dysentery, even though the infection may be eradicated, are always liable to attacks of looseness of the bowels, the gastrointestinal tract being very susceptible to slight irritations for a long time after.

CHAPTER II

IPECACUANHA AND ITS ALKALOIDS

Ipecacuanha or the 'Brazil root' was used in Brazil as a remedy for dysentery many centuries ago. In 1684, Piso first brought it to Europe. He discovered this valuable drug during his tour of exploration in Brazil and the West Indies, and on his return to Amsterdam he published an account of its anti-dysenteric properties. Piso's discovery failed to attract much attention except in Holland. The efficacy of the drug, however, was noticed by Helvetius who obtained a supply and sold it in Paris as a secret remedy for dysentery. He was fortunate enough to cure the Dauphin, the son of Louis XIV of France and after a few more successful trials, the French Government bought the secret from Helvetius. The remedy then came into use generally, but after its first vogue it seems to have been abandoned for a long time till the beginning of the 18th century when it became popular again. The powdered bark was given in 2 drachm doses with tincture of opium to prevent nausea and vomiting, and beneficial results were obtained in dysentery, tropical hepatitis and other conditions. The value of the remedy as a cure for dysentery became gradually established and in 1912 emetine, the alkaloidal active principle, came into use instead of the root.

The root is obtained from two species of *Cephaelis*, belonging to the natural order Rubiaceae. (1) *C. ipecacuanha* or the Rio ipecac (also known as *Psychotria ipecacuanha*). This is the only form recognised by the British Pharmacopoeia. (2) *C. acuminata* or *Carthagenia ipecacuanha* has a thicker root, its annulations are less marked and it is cheaper. The plant grows about 30 centimetres in height and is found in most parts of Brazil and is also cultivated in Minas Geraes and other provinces of that country. Attempts have been made to cultivate it in other places with some degree of success; from the Straits Settlements (Johore and Selangor are the most important exporting areas) ipecacuanha root of an unusually fine appearance and rich in alkaloidal contents is exported in considerable quantities. In Java and Ceylon the cultivation has not been so successful. Plantations were started in India in the Nilgiris, at Mungpoo near Darjeeling and at Mergui in Burma. The Darjeeling and Nilgiri plantations did not prove a success and have been practically abandoned. The Burma plantation is promising and is expected to yield roots of extremely rich qualities. The British Pharmacopoeia (1932) required that the root should not contain less than 2.0 per cent. of the alkaloids. The United States Pharmacopoeia allows both *Cephaelis ipecacuanha* (Rio) and *C. acuminata* (Carthagenia) to contain 7.75 per cent. of the ether-soluble alkaloids.

From the slender root and prostrated stem, roots are given off at intervals; some of these develop an abnormally thick bark and this thickened bark and thickened root constitute the drug of commerce. The root is gathered during the dry season, quickly dried in the Sun, and sifted from the adherent sand and earth. The official root is slender and tortuous, varying in colour from dark brick red to dark brown. It contains 2 to 3 per cent. of total alkaloids of which two-third is emetine; ipecacuanha wood yields about 1 per cent. of total alkaloids.

Substitutes of ipecacuanha in the market (1) *Ipecacuanha stem* has often been found mixed up with the root and much of the drug that is imported is a mixture of the two. It contains 0.97 to 1.8 per cent. of the total alkaloids, the yield being lower than that of the root.

(2) Under the name of East Indian root, the rhizome of a small monocotyledon plant *Cryptocoryne spiralis*, N.O. Aroideæ (Tamil-*Aithi Vadayam*) has been exported from Southern India (Madras), but the root contains neither emetine nor cephaeline. It resembles ipecacuanha root in appearance only.

(3) The root of *Psychotria emetica* or the greater striated ipecacuanha resembles closely the Brazilian ipecacuanha. It has been tried but although it has irritant and emetic properties, it contains no emetine.

(4) The roots of *Richardsonia scabra* occur in tortuous pieces, but they are quite different from those of the Brazilian ipecacuanha.

(5) White ipecacuanha is the root of *Ionidium ipecacuanha* N.O. Violaceæ.

(6) *Trinidad ipecacuanha*. Under this name the rhizome and root of *Asclepias curassavica* have been offered for sale.

(7) *Lesser striated ipecacuanha*. This drug is occasionally found in the market, and appears to be a species of *Richardsonia*.

(8) *Naregamia alata* (tin pani or titvel) grows in Western India and is said to have the properties of ipecacuanha, but it contains no emetine.

Many other roots also find their way into the market but with the exception of ipecacuanha stem none of them contains emetine or cephaeline. The following test for emetine is useful for distinguishing roots which contain that alkaloid from numerous substitutes.

Half a gm. of the powdered root is mixed with 20 c.cm. of strong hydrochloric acid and 5 c.cm. of water and filtered. To 2 c.cm. of filtrate 0.01 gm. of potassium chlorate is added; if emetine is present the liquid assumes a yellow colour changing to red in the course of an hour.

Chemistry of ipecacuanha. In 1817 Pelletier isolated the alkaloid emetine; in collaboration with Magendie its physiological action was determined and in 1829 it was first used in the treatment of dysentery. The discovery of emetine was quickly followed by the isolation of several

other important alkaloids strychnine, quinine and veratrine. These discoveries along with morphine so absorbed the attention of the profession that for the time being emetine was neglected. Pelletier's emetine contained the total alkaloids of ipecacuanha and this name continued till 1894 when Paul and Cownley showed that it consisted of two alkaloids to which they gave the names *emetine* and *cepheline*. Subsequently the same workers demonstrated the presence of a third alkaloid psychotrine which occurs only in small quantities. These three alkaloids are chemically closely related.

Emetine is a white amorphous substance which darkens on exposure to light, gradually assuming a yellow colour. Its halogen salts and nitrates are crystalline, the sulphate and the acetate are amorphous. The hydrochloride which is largely used is a white crystalline powder and is easily soluble in water and alcohol. Emetine is probably an isoquinoline derivative because the latter substance is formed on oxidation with potassium permanganate. It would therefore appear to be related to papaverine and narcotine; in fact some of the opium alkaloids have been shown to have a well-marked toxic effect on protozoa. Emetine is methyl-cepheline; iso-emetine is probably a stereo-isomeride of emetine, but attempts to convert one to the other have so far been unsuccessful. Iso-emetine is considered by some to be a methyl ester of iso-cepheline. Iso-emetine is non-emetic and comparatively non-toxic; it has, little effect in *E. histolytica* infections.

Cepheline is a crystalline alkaloid less soluble than emetine, it is soluble in alkaline solutions and darkens on exposure. By methylation, it is converted into emetine. Cepheline hydrochloride in doses of 1/12 to 1/6 grain is said to be a more powerful emetic than emetine.

Psychotrine is related to cepheline but has 2 atoms of hydrogen less. It is the least toxic of the three alkaloids and has a doubtful therapeutic effect in amoebic infection. On reduction, psychotrine yields a mixture of cepheline and iso-cepheline; these on methylation yield emetine and iso-emetine respectively.

Other constituents. An amorphous alkaloid has also been described as occurring in ipecacuanha. O-methyl-psychotrine and emetamine, two new alkaloids, have been prepared from ipecacuanha root; their proportions are 0.015 to 0.033 and 0.002 to 0.006 per cent. respectively; emetamine on reduction yields iso-emetine. Methyl-psychotrine has no action whatever on *E. histolytica*. The drug appears to be non-toxic to the patient in 2 to 9 grain doses but it is therapeutically inert. Dimethoxy-emetine has been prepared; it is less emetic and its general toxicity is also small. It can therefore be given in much bigger doses but it is less efficacious therapeutically than emetine.

Besides the three main alkaloids there is also another constituent, ipecacuanhic acid, which at one time was considered to be responsible for the action of ipecacuanha in dysentery. It has been shown however that

it is inactive. A crystalline glucoside ipecacuanhin has also been found in the root.

PHARMACOLOGICAL ACTION OF EMETINE

Amœbicidal action. Vedder (1911) found that emetine in dilutions of 1 in 100,000 killed living amœbæ in broth cultures and pointed out that 1 in 10,000 dilutions killed *E. histolytica* in pieces of mucus in stools, while 1 in 100,000 solution rendered them quite inactive in 3 minutes. Emetine was also said to be lethal to free-living amœbæ in dilutions up to 1 in 200,000 if the exposure was sufficiently long. *Entamœba gingivalis* is paralysed in culture by a 0.25 per cent. solution in four hours. Rogers (1912) confirmed Vedder's work and found that emetine was a very active drug, which attacked and quickly killed *E. histolytica* in dilutions of 1 in 100,000. He tried hypodermic injections of emetine hydrochloride in the treatment of amœbic dysentery with excellent results. Dale and Dobell (1917) demonstrated that even 1 per cent. solutions failed to have any effect on *E. histolytica* obtained from scrapings of the intestine of kittens infected with dysentery. The action is weak so that the encysted and the more resisting forms are not affected whereas the vegetative forms are killed. Allan (1920) found that emetine in dilution of 1 in 250 failed to kill *E. histolytica* in the stool of dysentery patients. Dobell and Laidlaw (1925) tested the action of ipecacuanha alkaloids on cultures of *E. histolytica* and found that emetine and cephæline of all the substances tested were able in very weak concentrations to kill the amœbæ, if allowed to act for a sufficient length of time. They prepared a special liquid medium for growing entamœbæ and added known quantities of the alkaloids to the tubes and thoroughly mixed them. The tubes were then inoculated with amœbæ and incubated for 2 or 3 days. These experiments made it clear that emetine even in dilutions weaker than those met with in the body after administration of a therapeutic dose had a toxic effect on *E. histolytica*, provided it was allowed to act long enough and the reaction of the medium was not too acid. Cephæline was also found to be definitely toxic for *E. histolytica*. Chopra and his colleagues found that *E. histolytica* present in mucus flakes lost their vitality and were eventually killed by emetine in dilutions of 1 in 200,000, provided the medium was alkaline.

It has been pointed out lately that there is a resemblance between *E. histolytica* and *Balantidium coli* in their reaction to emetine and cephæline; emetine has been shown to have curative effects in balantidial colitis.

Local action. The drug is a local irritant. Applied to the skin in high concentrations in the form of liniment it produces redness, itching and occasionally a pustular eruption; 1 in 500 solution causes marked irritation of the mucous surfaces. Some individuals are extremely sensitive to these effects and in them, urticaria and dermatitis may be pro-

duced by systemic administration of emetine. Application of a 1.0 per cent. solution to the abraded skin may produce a weal. When it comes in contact with the cornea it sets up a painful keratitis. Subcutaneous or intramuscular injections cause edema and hyperæmia of tissues and extensive capillary hæmorrhages in the muscle fibres round the site of injection. Unlike the cinchona alkaloids, no necrosis of tissues is observed and the action appears to be mainly on the walls of the capillaries and arterioles. A violent irritation of the bowels can be set up by irrigation with a 1 in 10,000 solution of emetine hydrochloride. Half a grain taken by the mouth produces nausea, quickly followed by vomiting in about an hour; an hour later loose stools are passed accompanied by griping. Much larger doses than can be borne by the mouth, are tolerated by injection without producing nausea, vomiting and diarrhœa; the effect would therefore seem to be purely local.

After injection, emetine can be detected in the stomach and intestines. Large doses of emetine given by injection cause swelling and congestion of the mucous membrane of the whole of the gastro-intestinal tract, which is often covered with mucopurulent secretion or studded with ecchymoses. In the dog, ulceration of the gut has been produced by giving emetine subcutaneously.

Gastro-intestinal tract. Chopra and his collaborators (1928) have shown that emetine inhibits the action of ptyalin even in 1 in 200,000 dilutions. Peptic digestion is, however, stimulated by concentrations stronger than 1 in 2,000, higher dilutions having no effect. Proteolytic and lipolytic digestions are inhibited by concentrations below 1 in 10,000; higher dilutions accelerate these. On the digestion of starch the action of this alkaloid is somewhat inhibitory. Emetine increases the tone of the non-striated muscle of the gastro-intestinal tract, the movements of the gut are stimulated, the effect being more marked as one passes downward from the stomach to the colon. It was also shown that the action was on the musculature directly and not through the nervous mechanism.

Circulation. On the heart of both cold-blooded and warm-blooded animals emetine has a markedly toxic effect. It depresses the excitability and conductivity of the heart muscle and produces slowing and dilatation of this organ resembling that produced by chloroform. The heart becomes irregular, auricular and ventricular dissociation may be produced, and death may occur from ventricular fibrillation, the heart stopping in diastole. In animals intravenous injections of large doses produce a marked fall of blood pressure; after small doses the pressure soon regains its normal level. The fall of pressure is due partly to the direct toxic action of the drug on the heart, but vasomotor paralysis is an important factor especially after large doses. In man there is an appreciable fall of blood pressure to the extent of about 20 mm. of mercury after an intravenous injection or after repeated doses by other

routes. Characteristic emetine pulse (weak, rapid and compressible) and cardiac irregularities of various types are seen after a series of injections of this alkaloid. The isolated heart is slowed and weakened by both emetine and cephaeline and it finally stops in diastole.

Non-toxic doses, while they lower the carotid pressure in animals, produce a rise in the pressure both in the pulmonary artery and vein. Larger doses dilate the pulmonary vessels. The coagulation-time of the blood is not altered though some think it is delayed. Emetine is toxic to the capillary endothelium producing petechial hæmorrhages; local application of emetine also gives rise to capillary hæmorrhage.

Respiratory system. There is some depression of the respiration after subcutaneous injections of the alkaloid, but after intravenous injections the respiratory centre is stimulated and the frequency and the depth of the respiratory movements are increased. Small doses increase the secretion of the respiratory passages and thus act as an expectorant. To this is added a slight relaxation of bronchial musculature which makes the removal of mucus easier. If toxic doses are given they have a decided tendency to cause pulmonary congestion or hæmorrhagic pneumonic consolidation.

Nervous system. In the frog, emetine causes a slowly advancing central paralysis. In mammals, neuritis is produced and there is general depression of this system giving rise to lethargy. The nerve cells especially those of the anterior cornua are damaged first and then the fibres degenerate; there is evidence that the motor fibres are specially picked out. Emetine has a powerful mental depressant action in man. Painful neuritis somewhat similar to that produced by alcohol has been observed.

Uterus. Emetine is said to produce stimulation of the uterine movements, but in dilutions such as those occurring in the body after its administration it has little or no effect.

Absorption and excretion. Emetine and the allied alkaloids are rapidly absorbed from the mucous membrane and the subcutaneous tissues, and are eliminated by the gastro-intestinal tract and by the kidneys. Elimination of emetine by these routes is demonstrated by the effect the drug produces in urinary and intestinal schistosomiasis. A part of the drug appears to be excreted by the bile which probably accounts for its curative effect in hepatic schistosomiasis and liver flukes.

Excretion by the kidneys is discontinuous and prolonged. The drug appears in the urine 20 to 40 minutes after hypodermic injection of a therapeutic dose, but during the course of treatment not more than one-sixth of the drug is excreted by this route. Elimination proceeds by fits and starts, active periods alternating with periods when little or none is found in the urine. The elimination in patients who have received 0.15 to 0.58 gm. in 3 to 6 days may last for 5 to 9 weeks, showing that it forms stable deposits in the body (Mattei 1920). In some cases the drug appears to have been retained for periods ranging

from three months to a year. Large doses irritate and produce inflammation and albuminuria together with chloride and nitrogen retention. The excretion of uric acid is increased by emetine as it is by other gastro-intestinal irritants.

Toxicity. The toxicity of emetine for lower animals has been worked out. By subcutaneous injections the lethal dose for dogs and cats varied from 0.003 to 0.005 gm. per kilo. body weight. If 0.003 gm. is taken as the maximum tolerated dose (corresponding to 0.210 gm. for a man of 70 kilo. or 145 pounds), it is apparent that the adult dose of $\frac{1}{2}$ to 1 grain is well within the margin of safety, provided the number of injections is restricted to 12 to 15. If this amount is exceeded and a much larger number of doses are given it is liable to produce severe reaction and even death.

With large doses, the changes produced in the tissues are of an acute nature, and immediate death within 24 hours may be produced with one single large dose. Doses of 0.05 to 0.075 gm. per kilo. in dogs, and 0.02 to 0.15 gm. per kilo. in rabbits, guinea-pigs, rats, etc., are rapidly fatal. With medium doses the pathological changes are more marked, more time being allowed for their production. With smaller doses it takes longer to produce the same pathological changes, indicating a cumulative action of the drug. There is probably no threshold of safety when the drug is taken continuously.

Emetine attacks all tissues and therefore is a general protoplasmic poison; changes in the kidney, liver, heart and skeletal muscles are identical, all showing hyperæmia, cloudy swelling and degeneration of the cells. The nerves do not show any detectable pathological change till the parent nerve cells are in a state of advanced degeneration. As animals do not manifest pain, probably the motor fibres only are affected. The only lesion seen in transverse section of the cord is degeneration of the anterior horn cells. Some authorities consider that the weakness of the muscles produced after emetine injections is due to the toxic action of the alkaloid on the protoplasm of the muscle fibres.

Pharmacological action of other alkaloids of ipecacuanha. The physiological actions of emetine and cephæline are very similar. Eggleston and Hatcher (1916) showed that cephæline is more irritant and about twice as toxic and emetic as emetine; their parasitocidal action on the entamoeba is about equal. It is generally stated that emetine has a stronger expectorant action and is a stronger nauseant than cephæline; its depressant action on the heart and its irritant action on the kidneys are more marked. Psychotrine is much less toxic but is likewise less parasitocidal. Ipecacuanhic acid, ipecacuanhin and various cephæline esters are more or less inert.

CHAPTER III

EMETINE IN AMŒBIASIS

Ipecacuanha has long been known as *Radix antidysenterica*. One of the chief uses of ipecacuanha is in the treatment of amoebic dysentery, and though emetine has largely replaced the powdered root, the latter is sometimes employed as a supplement to emetine injections. In old days, when ipecacuanha root was used, large quantities of the powder had to be given and it was difficult to avoid nausea and vomiting. Opium and morphine were employed to prevent those unpleasant accompaniments; powders were also used with keratin or salol coating which prevented the drug being dissolved in the stomach and allowed it to pass on to the duodenum, setting free the alkaloids in the intestines. These methods have now been superseded by the introduction of alkaloid emetine. Tull Walsh (1891) in a paper on the rational treatment of acute dysentery gave an account of the excellent results he had obtained with an average dose of one grain of emetine in 24 hours by the mouth. Vedder (1912) showed experimentally the high amoebicidal power of this alkaloid, both on the saprophytic and pathogenic amoebæ. Rogers (1913) started hypodermic injections of emetine as a routine treatment of dysentery and found that it had the effect hoped for by Vedder. Trials were initiated on a large scale and it was found that, though almost a specific for amoebic dysentery, it had little effect on the bacillary form. The oral administration of the powdered root was combined with emetine injections as it was thought that by this method the bowel could be thoroughly permeated with the alkaloid.

It may be said that both emetine and cephaeline, when given in adequate doses, produce a prompt disappearance of all the clinical symptoms of an acute infection with *E. histolytica*, and often a permanent disappearance of this organism from the stools. When given by the mouth, however, they produce nausea and vomiting and are often not retained. Emetine has

therefore to be administered in the form of injections and it preferably should be given intramuscularly on account of the tendency it has to produce local inflammations and hæmorrhages after hypodermic injections.

(1) The literature on the use of emetine in the treatment of amoebic dysentery is very extensive, various writers giving different quantities and in different set courses. Knowles (1928) summed up these papers and said that the general consensus of opinion appears to be:—(a) that emetine injections are by far the most satisfactory immediate line of treatment of amoebic dysentery, but (b) that emetine therapy is generally a failure in the treatment of the carrier condition. It has been shown that primary malaria, as therapeutically induced in the treatment of general paralysis of the insane, is a disease which is readily amenable to quinine treatment; only a few days of quinine treatment are necessary to effect a cure without relapses. On the other hand, the experience of all workers in the tropics is that established and relapsing malaria is very difficult to eradicate. Possibly a similar state of affairs exists with regard to amoebic infection of the gut; the prospects of eradicating the infection by emetine therapy may be much better in patients seen when suffering from the first attack of amoebic dysentery than in cases where the infection has become chronic and is well established. In a series of 32 acute and chronic dysentery cases which had 6 to 9 grains of emetine by daily injections of 1 grain each, the ratio of probable cures to failures worked out as 1 : 1.7. The cost of treatment roughly estimated was 2 to 3 rupees per head. These results are similar to those obtained by other workers. Emetine injections undoubtedly eradicate an infection with *E. histolytica* and apparently the alkaloid is more effective in acute amoebic dysentery than in cases of chronic amoebic colitis. In the majority of chronic infections, however, the injections do no more than clear up the symptoms and these patients generally become carriers.

(2) Rogers (1929) recommends daily injection of 1 grain for not more than seven or eight days. He follows the treat-

ment by 20 to 30 grains of ipecacuanha with 10 grains of tannic acid (to lessen the danger of vomiting) and a drachm of mucilage in one ounce of water, to be taken last thing at night before going to bed, and repeated each night for a week. By this method the organisms in the tissues as well as those in the bowels are acted on by the drug.

(3) Deek's treatment consists in giving emetine injections combined with large doses of bismuth salts orally. Knowles (1928) analysed a series of 55 cases treated with daily injections of emetine combined with one drachm of bismuth carbonate by the mouth every day. The patients were suffering both from acute and chronic symptoms, the majority belonging to the latter class. The ratio of probable cures to failures in this series was 1: 1.8. These results are not very encouraging but there appears to be little doubt that bismuth treatment, in combination with emetine injections, from the clinical point of view at any rate, gives good results. The results so far as eradication of the infection is concerned are disappointing.

(4) Emetine injections have also been used in combination with such other drugs, as *Holarrhena antidysenterica* bark, yatren, stovarsol, etc.

Acute and sub-acute amœbic dysentery. The following procedure for treatment of such cases has been recommended by Acton and Knowles:—The patient is kept strictly in bed and made to use the bed pan. A saline purgative is given in the morning to flush the colon; some prefer to give an initial dose of castor oil or castor oil combined with opium (castor oil $\frac{1}{2}$ oz. or 15 c.cm., tincture of opium 15 minims). The diet should be light, chiefly milk or boiled fish. Emetine injections are either given alone or combined with bismuth by the mouth, 1 to 2 drachms of bismuth carbonate is given every four hours in half a glassful of water during the day, with the object of decreasing the acidity of colon and increasing the alkalinity of the portal blood. Some recommend a heaped teaspoonful (180 grains) of bismuth subnitrate in a tumbler of water every three hours night and day in severe cases. Two and a half hours after the first dose of bismuth an injection of 1 grain of emetine hydrochloride is given. The timing of the injection is important as it has been

shown that emetine acts best in an alkaline substrate and that the alkalinity in the portal vein rises about that time. This treatment is carried on for nine consecutive days. For the next three days emetine and bismuth are suspended and only a saline purgative is given. The complete treatment with saline, bismuth and emetine is again repeated for 3 to 6 days. The stools should then be examined for at least 6 consecutive days, preferably 8. This is not always possible for the patient thinks he is cured as soon as the symptoms abate and leaves the hospital.

In case of acute or subacute types of amoebic dysentery, the author has obtained very satisfactory results by the following line of treatment. The patient is kept confined to bed with a flannel abdominal binder and put on light liquid diet, preferably barley water or lime whey. Emetine is given intramuscularly in 1 grain doses daily for six consecutive days. After an interval of three days, a second series of three injections should be given in daily doses of 1 grain. Bismuth carbonate in two drachm doses thrice daily is given throughout the course.

In acute cases with severe pain and tenesmus give a hypodermic injection of $1/6$ grain of morphia, or a small enema of opium and starch (tinct. opii 40 minims or 2.5 c.cm., mucilage of starch 1 oz. or 30 c.cm.). Hot applications to the abdomen such as turpentine stupes, or poultices consisting of linseed meal with a little mustard are soothing. The patient should be kept warm.

Emetine in relapsing and chronic dysentery. Chronic and relapsing amoebic dysentery is one of the common diseases of the tropics and one of the most difficult to treat. Theoretically emetine should be an ideal drug against amoebiasis, as after injection the alkaloid is excreted in the gut and should thus destroy most of the amoebæ. In actual practice, however, it has not proved uniformly satisfactory and a large number of cases relapse. It is said that emetine cures about one-third of the cases; one-third apparently improve and in the remaining one-third the drug has no effect at all. Brown (1926) at the Mayo Clinic found ipecacuanha and its derivatives effective in 58 to 70 per cent. of cases as shown by repeated examination of

stools. The reason for this failure in some cases is the fact that, although emetine acts on the amœbæ lodged in the tissues of the intestinal wall, it has no effect on the parasites in the lumen of the gut. It is known that non-pathogenic amœbæ like *E. coli* remain on the surface of the mucous membrane and possibly *E. histolytica* may do the same though, as a rule, the parasites are found in the tissues. They gain access to the radicles of the portal vein and are carried to the liver where they set up hepatitis and abscesses. Local applications such as colonic irrigation are therefore ineffective. The deeply situated organisms are only reached by emetine through the blood stream. Unfortunately in long-standing cases fibrosis is set up and the capillaries are cut off, thus preventing the access to the parasites of the drug circulating in the blood. Entamœbæ lying in the necrotic or fibrotic tissue (which is avascular) are thus liable to escape the action of emetine. This is the reason why many chronic cases are not amenable to treatment. The second factor is the infection of the ulcers with *B. coli* and other intestinal bacteria which further promote these pathological changes and lead to the chronicity of the lesions, thus hindering the curative action of emetine. Association with dysentery bacilli is not uncommon and some observers go so far as to say that the lesions of amœbic dysentery are not due to *E. histolytica* alone, but to a combination of amœbic infection with some bacterial organisms. Recently, chronic and relapsing cases of amœbic dysentery have been found to be associated with *Bact. pseudocarinatus* which is said to be a phage-modified variant form of Flexner bacillus. The presence of this bacterium along with *E. histolytica* undoubtedly intensifies the symptoms and renders cure more difficult. *B. mucosus* has been cultivated from the ulcers of a number of fatal cases and Acton has pointed out that streptococci play an important role. For these reasons infection with entamœbæ if not treated thoroughly in the early stages is always likely to pursue a chronic course, when it requires prolonged treatment.

Briefly the difficulty of curing chronic amœbic dysentery is due to four factors :—

- (a) Emetine is a toxic drug and it is not possible to give

it in sufficient amounts and over sufficiently prolonged periods to destroy all the parasites. Chronic infections are resistant to treatment though relief of symptoms occurs in the majority of cases. (b) Emetine cannot be brought into contact with amœbæ deeply seated in the ulcers by colonic irrigation. (c) The presence of secondary bacterial infection is an additional factor in preventing cure. When amœbic and bacillary dysentery especially of the Flexner type co-exist, the reaction of the gut becomes very acid and emetine cannot exert its full therapeutic activity. (d) In bacillary dysentery (Shiga type) the reaction of the gut may be alkaline to litmus (pH 8.11), in the amœbic form the pH of the stools is 6.3. It is found that when the pH of the contents of the gut is 7.0 the amœbæ are dead or dying; cyst formation occurs when the pH of the contents is 7.24; Charcot-Leyden crystals are passed at 6.96. The acid reaction hinders emetine which acts better in an alkaline medium. Attempts at markedly raising the alkalinity of the contents of the large intestine by giving alkalies by the mouth have not met with much success. The drugs which decrease the acidity of the contents of the large intestine are compounds of bismuth, preferably bismuth carbonate. (Deck's method).

If energetic treatment is not started in the early stages before extensive destruction of tissues has taken place, relapses are almost certain to occur. There is little doubt that the secondary bacterial infections probably account for most of the cases of failure with emetine. Resistant chronic cases of amœbic dysentery are not infrequently benefited with vaccine, made from such organisms as streptococci, dysentery bacilli, etc., previous to emetine injections. Emetine is much more efficacious in the early than in the later stages of dysentery. The drug is only feebly active against the encysted amœbæ, which though themselves quite harmless, indicate active vegetative forms in the tissues. In cases of relapse, a course of emetine bismuth iodide, 3 grains daily for 12 days may bring about a cure. Dobell and Low (1922) recommend a 'double course' of this drug—3 grains (0.2 gm.) daily for 24 consecutive days, but in the writer's experience in India

very few persons can tolerate such large doses. In the Carmichael Hospital for Tropical Diseases, Calcutta, a course of 1 grain of emetine daily for 10 days was successful in curing a large number of chronic cases of amœbic dysentery. An alternative method is combined treatment with emetine hydrochloride by injection and emetine-bismuth-iodide by the mouth. Emetine hydrochloride is given in one grain doses with emetine-bismuth-iodide 2 grains daily for 6 to 9 days. Even this proved a failure in quite a large percentage of cases. James and Deeks combine emetine injections with bismuth subnitrate, one heaped teaspoonful (180 grains) 3 or 4 times a day, which may be continued for 2 to 3 months after the injections have been stopped. It has been shown that emetine fails to prevent cyst formation especially when the atmospheric temperature is high. Encysted parasites therefore occur in the gut for long periods.

In a number of cases the infection is not eradicated and often the cure is only an apparent one, cysts and Charcot-Leyden crystals being present in the stools. When infection is not eradicated the patient may suffer now and then from attacks of amœbic diarrhœa, or he may have constipation alternating with periods when he passes blood and mucus with stools. A patient in the carrier condition may at any time develop acute amœbic dysentery. An infected person frequently suffers from periodic attacks of acute amœbic dysentery when only the large tissue-invading forms of *E. histolytica* are present in the stool. Between the attacks when acute symptoms have abated, the carrier condition is maintained. In such cases the courses of both emetine and emetine-bismuth-iodide will have to be repeated after a suitable interval, allowing for all the emetine to be excreted which usually takes 1 to 2 months after a course. The drug treatment of amœbic dysentery should be controlled wherever possible by sigmoidoscopic in addition to microscopic examinations.

Fletcher and Jepps (1924) carried out autopsies on amœbic dysentery cases, and found evidence of the healing power of emetine on amœbic ulcers. In the majority of cases a 12 days'

course of emetine is sufficient to ensure complete healing of the ulcers.

There is no doubt that patients passing *E. histolytica* cysts, especially those who show thickening and tenderness of the cæcum as a result of repeated attacks, should be submitted to repeated treatment with emetine because they have active amœbic lesions as can be demonstrated by the sigmoidoscope. In the cases of healthy cyst carriers discovered on routine examination treatment is not necessary. Due care, of course, should be taken regarding the disposal of their fæces to prevent the spread of infection.

Amœbic hepatitis and liver abscess. Duncan (1902) stated there was no relationship between tropical liver abscess and any form of dysentery. Rogers (1902) showed that living *E. histolytica* could always be found in scrapings from the walls of such abscesses and further that clinical and post-mortem evidence showed that they were secondary to dysentery, always of amœbic origin, but commonly limited to the cæcum and ascending colon which usually gave rise to no symptoms at the time of liver abscess formation. He was of opinion that open operation should be avoided as it always led to secondary septic infection. Chevers (1886) first advocated large doses of ipecacuanha treatment combined with aspiration of liver abscesses on a scientific basis. Later, emetine injections replaced ipecacuanha.

Presuppurative hepatitis. The acute type of hepatitis is easily recognised, and in this emetine gives striking results. In this type aspiration is dangerous and may produce fatal results from internal hæmorrhage. Acute hepatitis with multiple small abscesses is indistinguishable clinically from the above condition. The liver is riddled with scores of small abscesses varying from the size of a pea to that of a walnut. These may clear up under emetine treatment.

Chronic presuppurative amœbic hepatitis is difficult to diagnose and frequently goes on to abscess formation if care is not taken. The liver may not show any tenderness or pain and active dysenteric symptoms are nearly always absent. There may not even be a history of dysentery owing to very limited ulceration confined to the cæcum. In the majority of fatal cases

of liver abscesses Rogers found a very slight degree of amœbic ulceration and in some cases only scars of former ulcers. Leucocytosis with a marked increase in the polymorphonuclear cells is always present and often the condition is only recognised from this. In the absence of fever where leucocytosis is present the condition should be suspected. X-rays may be of value in diagnosis but they do not always reveal abscess formation when it is present in the liver substance. This presuppurative stage may last for a month or longer. Amœbic hepatitis is common in areas where amœbiasis is endemic. According to some authorities 'tropical liver' which is neither amœbic nor alcoholic in origin may result from residence in a hot climate and for this treatment with ammonium chloride is recommended. Such a procedure would be dangerous and it is advisable in all doubtful cases to begin with emetine. That large amœbic abscesses are absorbed under emetine is supported by post-mortem evidence of extensive scars in the liver. Undoubtedly large bulging abscesses diagnosed by putting a needle and drawing out pus have cleared up under emetine.

The fully developed abscess is usually circumscribed by a dense fibrous wall which prevents further destruction of the organ. In certain very acute and actively spreading abscesses there is no limiting wall, small points of suppuration in the branches of the portal vein invaded by living amœbæ are seen round the irregular cavity. The amœbæ are found in an active stage in the wall of the abscess, those which are cast off soon die. This is the reason why living amœbæ cannot be found in the pus, but they can always be found in the scrapings from the wall. These amœbæ are destroyed by injections of emetine. The mortality from liver abscess was very high in pre-emetine days owing to the inevitable secondary infection after an open operation.

Amœbic liver abscess. It has already been observed that emetine is excreted in the bile; it therefore acts on the entamœbæ present in the liver. In amœbic hepatitis, commonly met with in India, emetine is a powerful agent preventing the development of an abscess. After the formation of an abscess, some authorities maintain that it is necessary to aspirate the pus and inject

emetine hypodermically till 7-12 grains have been given. Others consider aspiration unnecessary and say that the pus is absorbed after emetine injections. Cases of amœbic abscess of the liver have undoubtedly been successfully treated with emetine injections only. Manson-Bahr and others have recently confirmed that emetine therapy can by itself promote absorption of pus from a liver abscess without surgical interference. Amœbæ, it is held, are killed in the liver by emetine. The abscess in the active condition has a zone of hyperæmia round it and so long as amœbæ are alive the flow is from this zone towards the abscess. As soon as the amœbæ are destroyed by the action of emetine, the current as regards the abscess is reversed, and the result is absorption and extinction of the abscess. The absorption of sterile pus is in no way detrimental to the patient. There is no doubt that the incidence of abscess of the liver has considerably decreased since the use of emetine in amœbic hepatitis. Neither the gravity of the condition of the patient nor the size of the abscess are contraindications to treatment with emetine. The only disadvantage is that the absorption sometimes takes several weeks and this may weaken the patient. The only indication for surgical interference is the presence of bacteria in the aspirated fluid. It is very rare to find bacteria in unopened abscesses and when they are present the conditions are probably not amœbic but due to extension of a suppurative process from the peritoneum or pleura.

That emetine has some stimulant action on the liver cells can be judged by the fact that it has a beneficial action in other conditions where functions of this organ have been deranged. The writer has found emetine useful in chronic hepatitis of malarial origin, catarrhal jaundice and chronic congestion of the liver due to causes other than heart and kidney diseases. The cholagogue action attributed to emetine has not been confirmed by experiments.

Emetine, however, has been wrongly used in conditions simulating amœbic abscess of liver for want of proper diagnosis. The author has seen cases of chronic malaria given 20 to 30 injections of emetine because the symptoms resembled those of amœbic hepatitis. Although rigorous scientific proofs regarding the

existence of primary amœbic infection of the lung and bladder are not forthcoming, emetine injections cure these conditions when *E. histolytica* is found in them. Amœbic cholecystitis has been proved by finding amœbæ in the pus from the gall bladder.

DOSAGE AND MODES OF ADMINISTRATION

Dosage. The treatment with emetine must be continuous if it is to be efficacious. It must be prolonged for a sufficient period and the dosage should be adequate. Intermittent treatment with small doses or only for a few days may relieve acute symptoms but will not eradicate infection. On the other hand it should be remembered that emetine is a highly toxic substance and if given in large quantities it may produce severe diarrhoea, heart trouble, great prostration and even collapse and death. The consensus of opinion at the present time is that under no circumstances should more than twelve injections of one grain each daily be given in one course, as they are liable to produce toxic symptoms. In the majority of cases 9 injections suffice though many authorities prefer a larger number. The course can however be safely repeated after an interval of 3 to 4 months. Deutsch (1928) recommends for 6-months-old infants a dose of 0.01—0.02 gm., for one-year-old 0.03—0.05 gm., total quantity up to 0.12 gm.; for yet older infants up to 0.15 gm. by injection. As the drug is excreted slowly from the system, with continued administration the dose should gradually become smaller. Vomiting may result but is not serious. The dose must be smaller for weak infants. Cawston (1929) thinks that prolonged administration of relatively small doses of emetine is more to be feared than a few heroic doses and that the immediate toxic effects of the drug are less dangerous than those due to cumulative action. The use of larger doses on alternate days has therefore been suggested, as this would enable the system to recover from the toxic effects of one dose before the next is given and thus avoid further doses as soon as the earliest signs of cumulative action are recognised.

By mouth. Oral administration of ipecacuanha powder was recommended in old days to follow the course of emetine injections; 20 to 30 grains of the powder were given with 10 grains of tannic acid in a drachm of mucilage and an ounce of water, three hours after a light meal and before retiring. This was repeated every night for one week. The usual practice was to begin with a larger dose such as 30 to 40 grains (2 to 2.7 gm.), then to decrease it nightly by 5 grains until a 5-grain dose was reached, which was continued for a week or longer if necessary. As a rule nausea and vomiting were constant accompaniments. About the middle of the course diarrhoea with canary yellow coloured stools appeared and this was looked upon as a favourable sign. In acute cases blood and mucus rapidly disappear and after the course the stool becomes normal. As the root powder contains many superfluous ingredients and is as irritant as emetine, it has now-a-days been superseded by the pure alkaloid.

Emetine hydrochloride is as effective when given by the mouth as by any of the other routes; it is completely absorbed from the gut. Various devices have been adopted to reduce or abolish its nauseating or emetic effects. Unfortunately these have never succeeded without at the same time diminishing or annulling its therapeutic action. Pills and tablets coated with keratin, stearin, salol or other insoluble substances usually minimise the nauseating effects of emetine, but these may not dissolve in the gut and therefore produce no therapeutic effect. The best method of giving emetine by the mouth is as emetine-bismuth iodide. If emetine has to be given by the mouth the dose should not exceed $\frac{1}{4}$ grain. The drug has been administered in various ways, the object being to hurry its passage through the stomach so that the nauseating and emetic action of the alkaloid is avoided. Fuller's earth adsorbate or alkresta tablets have been recommended by some. Keratin-coated tablets have to be used at night before going to bed, the same precautions being taken as in the case of ipecacuanha treatment. Sometimes a certain amount of tolerance develops—the patient retaining the drug after rejecting it for the first 2 or 3 days; 10 to 15 minims of tincture of opium administered previously may

diminish or abolish vomiting. As a rule in acute cases where the patients have to be kept in bed, injections are the best; in chronic cases with slight local lesions the oral method may be employed. Administration of ipecacuanha direct into the duodenum by catheter has been tried.

Per rectum. Good results are said to have been obtained by enemata of 4 to 8 gm. of ipecacuanha powder suspended in a pint and a half of water. Sellards and Levia (1923) strongly advocated the administration of emetine per rectum and recorded actual work on experimentally infected kittens. Colonic irrigations of 0.1 gm. of emetine in 1,000 c.cm. of water or saline have been employed but they are irritating. Preparations like 'emetol' and 'paremetol' for rectal administration have been put on the market. This method, however, is not very suitable for private practice and its practicability also appears to be doubtful, because in man such injections under ordinary circumstances would not go much further than the splenic flexure. Besides, emetine is very irritant to the mucous membrane without having greater amoebicidal virtues *in vitro* than quinine, silver nitrate, etc. This method therefore is not recommended in ordinary cases.

Subcutaneous and Intramuscular injections. Emetine is given either subcutaneously or intramuscularly. The drug is less irritant and painful when given by the latter route owing to smaller number of sensory nerve endings there. Acton and Chopra (1924) showed that emetine injections in rabbits produced œdema and congestion of the tissues at the site of injection, and extensive petechial hæmorrhages but no necrosis. Many authorities recommend $\frac{1}{2}$ to $\frac{1}{4}$ grain (0.02 to 0.03 gm.) as the average dose for an adult by daily injections. The total in any series of injections should not exceed 12 grains on account of the cumulative effects and especially the production of polyneuritis. Some individuals develop an idiosyncrasy towards the drug, a considerable amount of pain and stiffness being caused when given by any of these routes. The symptoms last for several days, and even when injections are given into the loose cellular tissue of the abdominal wall, considerable redness and small hæmorrhages are found at the site of injection in spite of

all precautions to secure proper sterilisation of the skin and needle while other patients under the same conditions develop no trouble whatsoever. These facts should be borne in mind in the treatment of individuals who are not confined to bed, as pain and stiffness may prevent the patient from using his arm for several days. Pain caused by emetine is diminished by dissolving it in a 1.0 per cent. solution of carbolic acid.

Intravenous route. This method was rarely employed formerly but it has come into vogue recently. As early as 1913 intravenous injections of emetine were tried; but toxic symptoms were not uncommon; these consisted of dyspnoea, vomiting, diarrhoea, very slow pulse, unconsciousness and muscular paralysis. Petzetakis (1924) advised emetine intravenously in the treatment of severe cases of amœbiasis; beginning with 0.03 to 0.05 gm. on the first day, and reaching a maximum of 0.1 gm. on the fourth day, a total of from 0.5 to 0.6 gm. of emetine was given in 10 days. In chronic cases also good results have been obtained.

The drug when given by this route should be well diluted and administered very slowly. The dose should not exceed $\frac{1}{4}$ to 1 grain (0.015 gm.) dissolved in at least 10 to 20 c.cm. of sterile saline. Concentrated solutions have been given but weaker solutions are preferable. It is advisable to have an ampoule of adrenalin ready so that it can be given at once if there are signs of cardiac depression or vasomotor paralysis. Some authorities give $\frac{1}{2}$ to 1 grain, nine injections being followed by an interval of 6 days, after which 6 more injections are given making a total of 15 grains. Intravenous injections are likely to be followed by nausea and vomiting which may supervene $\frac{1}{2}$ to 1 hour after administration. The results are said to be rapid and striking and superior to those from intramuscular or subcutaneous injections. De Castro and Deuskar (1927) found that intravenous injections did not give any better results than subcutaneous and intramuscular injections and the experience of the author is the same. Intravenous injections undoubtedly throw more strain on the heart and they should be given with caution especially when that organ is diseased.

CHAPTER IV

COMPOUNDS OF IPECACUANHA AND EMETINE

As emetine, when given by the mouth, produces vomiting, certain insoluble preparations which pass through the stomach unchanged without liberation of the alkaloid have been introduced. Besides these, certain preparations for rectal use have also been prepared.

(a) **Emetine adsorbate or Alkresta Ipecac.** (Lilly & Co.) Alkresta ipecac is the trade name given to an adsorption compound of the total alkaloids of ipecacuanha with hydrated aluminium silicate (Fuller's earth). It is made up in tablets, each of which contains the total alkaloids of 10 grains of ipecacuanha, U.S.P. The advantage claimed for this form of emetine is that it passes through the stomach unchanged and the alkaloid is liberated in the alkaline intestinal contents. This is doubtful. It is now claimed that some of the emetine is dissolved in the intestine in some other way, perhaps by the bile or soaps present there and is absorbed. No exact data are available but it is said that the clinical as well as systemic effects of this form of emetine are not marked. The dosage recommended is 2 to 3 tablets three times a day.

Allan (1916) treated 10 cases with alkresta tablets and found the drug unsatisfactory on account of the variation in absorption from the intestinal tract. He thought emetine subcutaneously was twice as effective. Stephen and Mackinnon (1917) treated 81 cases, all carriers. They gave 10 tablets daily for 14 days, 5 in the morning and 5 in the evening. They concluded that the drug gave better results than injections of emetine hydrochloride. Macgregor and Frew (1922) treated 15 cases of old-standing chronic infections with 2 permanent cures. They gave 30 grains orally combined with daily injections of emetine. Knowles (1928) in a series of 7 cases found alkresta on the whole unsatisfactory. The drug could occasionally eradicate infection with *E. histolytica* but on the whole the results were disappointing. The drug is well tolerated by the patients and its administration is not followed by nausea or vomiting as is the case with emetine bismuth iodide. It is best given at bedtime and is a suitable preparation for private patients. It is worthy of trial in chronic amoebic dysentery.

(b) **Emetine-bismuthous-iodide (E. B. I.).** Dose 3 grains (0.2 gm.) containing approximately 1 grain (0.06 gm.) of emetine. Tull Walsh (1891) first thought of combining emetine with mercury and iodine and made emetine-mercurous-iodide. He

treated 22 cases with this compound but the results were not satisfactory. Du Mez (1915) manufactured emetine mercurous iodide and emetine-bismuthous-iodide and suggested, as results of his experiments on dogs, that these two compounds might be given in large and frequent doses, which would enable emetine to come in contact with *entamoebæ* for prolonged periods. Emetine-bismuthous-iodide is a brick-red powder, insoluble in water. In acidulated water it does split to a certain extent, as is evident from the fact that in 0.2 per cent. solution of hydrochloric acid an opalescence is noticed. The double iodide is perfectly stable in air. According to Du Mez's calculations it contains 58 per cent. iodine, 12 per cent. of bismuth and 29 to 35 per cent. of emetine.

It is advisable to give the double iodide as a loose powder in a hard gelatine capsule or paper cachet. It should not be given in hard or compressed tablets or mixed with insoluble excipients such as vaseline, soap, stearin, etc., nor should it be coated with keratin, salol or other more or less insoluble substances. Experience has shown that unless properly protected it is liable to be dissolved in the stomach giving rise to the usual irritant symptoms of emetine. Even keratin coating was found to be uncertain as nausea and vomiting were produced. In the presence of the alkaline contents of the duodenum the compound readily decomposes, loses its red colour and becomes opalescent white. A 3 grain (0.2 gm.) dose of the insoluble salt containing about one grain of emetine, is the average dose and 10 to 12 such doses are to be given in succession. Indian patients can rarely stand more than 2 grains daily. This is the standard 'full course' which was found to be very successful. Some prefer to give the drug in cachets of one grain each three times a day until 36 grains (2.4 gm.) have been given as larger doses very often are not tolerated. Vomiting when it occurs does not come on as a rule until some time after the dose, indicating the probable liberation of emetine from the intestine and not from the stomach. It is recommended by some authorities that the dose be given after a full meal when the stomach contents would certainly be acid, and on the whole administered in this way the drug is well tolerated.

Others prefer to give it on an empty stomach, and are of opinion that it causes less nausea. The dose should be given at night when the patient is in bed and resting quietly, preferably with a cup of hot tea or arrowroot. The patient should endeavour to sleep and the saliva should be wiped from the mouth or expectorated and not swallowed. In many cases there is vomiting on the first night, but this does not matter if the powder is not rejected; on the second night there is usually little or no vomiting. Throughout the course there is a tendency to slight vomiting in many patients though a certain amount of tolerance does undoubtedly develop for the drug. If nausea or vomiting becomes troublesome it is necessary to give 15 minims (1.0 c.cm.) of tincture of opium, or chlorodyne, or omuopon $1/6$ of a grain, half an hour before each dose. Hot applications or a mustard plaster to the epigastrium may also help. To obtain satisfactory results reduction of the daily dose and intermission or shortening of the course of treatment must be avoided and treatment should only be stopped if severe prostration or cardiac depression supervenes. Emulsions of emetine-bismuth-iodide in 1 ounce of liquid paraffin have been tried and are said to have given better results than tablets.

As the treatment of the carriers with emetine or ipecacuanha during the Great War gave very unsatisfactory results, emetine-bismuthous-iodide was investigated. Cats weighing 3 kilograms could stand doses up to 40 mgm. without vomiting. The drug was then tried in 10 human carriers, but it produced vomiting and diarrhoea. Dobell (1918) reported treatment of 11 carriers who had not been cured by injections of emetine. In all these cases the treatment was successful. He showed that an advantage is gained by administering emetine in the form of emetine-bismuth-iodide in chronic cases which have proved refractory to emetine. The effects of treatment are in some cases remarkable and all stages of *E. histolytica*, whether cystic or otherwise, disappear from the stools. Emetine-bismuth-iodide was thought to be almost a specific against *E. histolytica*, and 2 or 3 courses were necessary to effect a complete cure. It should be noted also that if the first course fails to effect a cure a second course consisting of the same amount of drug administered for the same length of

time is practically never efficacious. Both the dosage and the duration of treatment must be increased for the second course. Although undoubtedly failures after such courses have been reported, the chances of curing carriers of *E. histolytica* with this drug are greater than with emetine in the form of any other salt. Treatment must be regulated by carefully watching the patient who should be kept strictly in bed. In acute cases this is not difficult but patients who are carriers and have no definite symptoms may object. If rest is rigidly enforced there is less sickness and there is less liability to heart trouble. Light diet is of importance throughout the course of treatment. Emetine-bismuth-iodide generally produces diarrhœa about midway or a little later in the course; this is often beneficial as it keeps the bowel thoroughly cleared in addition to the specific effects of the drug. Towards the end of the course depression and general weakness are noticeable, and in some cases the heart sounds may become very feeble and irregular. The pulse should be felt daily and when this condition is detected the drug should be stopped. When the course is over the patient quickly recovers, diarrhœa ceases and the stools become solid.

Emetine-bismuth-iodide is thought by some to be less efficacious in acute dysentery than hypodermic injections of emetine hydrochloride, but Dobell and Low (1922) consider the compound to act equally well in acute cases, in carriers, and in all intermediate conditions. Lambert (1918) treated 40 Indian cases in Mesopotamia and came to the conclusion that in acute cases combined treatment, *i.e.*, emetine injection and emetine-bismuth-iodide by the mouth is the best. In relapsing cases and carriers emetine-bismuth-iodide alone is better. He considers that in emetine-bismuth-iodide we have a combination of considerable potency in the treatment of amœbic dysentery, preferably when the amœbæ are assuming their resistant stage. He recommends it in 2 grain doses every night for debilitated patients. Rennie (1922) tried the drug on 87 cases with good results. Delayed vomiting indicates that the drug is beginning to take effect. During the course, diet should be light and restricted. Manson-Bahr and Sayer (1927) state that many which fail to respond to emetine injections respond to

emetine-bismuth-iodide. They are of opinion that the introduction of this drug has considerably raised the percentage of cures in chronic amoebic dysentery. They admit, however, that such treatment is not ideal from the patient's point of view and there is need for a less toxic and more efficient drug. The well-known toxic effects of emetine are also an objection to its use. Jepps had only 12.7 per cent. of failures with 3 grain doses in an emulsion of $\frac{1}{2}$ ounce of liquid paraffin floated in 2 or 3 ounces of water. The degree of tolerance of patients to the drug varied considerably.

It will be seen, therefore, that while emetine-bismuthous-iodide is a useful drug and worthy of trial especially in chronic cases, it leaves a large residue of cases in which the infection is not eradicated even after several courses. The treatment with emetine-bismuth-iodide is drastic but is said to cure 70 to 80 per cent. of cases of chronic carriers. When once a patient has resisted three courses of emetine-bismuth-iodide, it is no use persisting with it. Sometimes combination of the drug with vaccine made from bacteria infecting the ulcers may be useful. It may also be said that, the hope that the relative insolubility of the drug would prevent vomiting, which is a very annoying, tiresome and unpleasant complication in treatment, has not altogether been fulfilled. It is possible that some detail of administration has yet to be discovered which will remove this objection. The drug is very useful in treatment especially of chronic amoebic ulceration and is worthy of trial where emetine injections have not succeeded.

(c) **Emetine periodide** (E.P.I.). The dose is 2 grains (0.13 gm.) thrice daily after food. The course lasts for 15 days. It is usually combined with 5 grains (0.3 gm.) of exsiccated ox bile which is said to increase its action.

This compound introduced by Martindale, contains 38.7 per cent. of emetine and 61.3 per cent. of iodine. In the presence of acids no emetine is liberated, while in the presence of 2 per cent. sodium bicarbonate the compound is decomposed setting free emetine. It is a dark purple crystalline powder, insoluble in water and physiological acid (0.2 per cent. HCl); it is readily soluble in acetone and slightly soluble in alcohol, chloroform and ether. Clinical experience shows that it is the least toxic of the emetine preparations and as much as 120 grains have been given in 20 days without toxic manifestations, which not un-

commonly occur with emetine-bismuthous-iodide. It is said to be as effective as emetine-bismuth-iodide. If necessary, the course can be repeated after ten days. From the patient's point of view it is more satisfactory than emetine-bismuth-iodide, as nausea, vomiting, depression and weakness are almost entirely absent. Willmore (1923) tried it in a number of refractory cases with good results. He considered it desirable to combine it with medication per rectum especially in those cases where ulceration of the lower bowel is present. It has been combined with stovarsol; it has also been given in sprue, cholera, typhoid fever, etc. Its oral use is said to clear up the urine in children intensely infected with *S. haematobium* as rapidly as emetine injections. Emetine periodide, however, does not cure every case of the disease and when once a person has resisted 3 courses of the drug it is of no use persisting. In amoebic dysentery an intensive course of 90 grains in 15 days is suggested, repeated if necessary, after 10 days. For use in the tropics, a preparation of emetine periodide in dried milk has been recommended (1 grain in 2 drachms of milk), two teaspoonfuls of this being taken in 30 ounces of warm water.

Emetine periodide has been used by many clinicians along with a course of emetine injections. Such a course consists of six injections of emetine, 1 grain each on alternate days combined with 2 grains of emetine periodide concurrently given three times a day with 5 grains of oxbile in separate capsules for 15 days. Given in this way the drug is said to be more effective and less toxic than emetine-bismuth-iodide, and superior to emetine, yatrien or stovarsol alone. The consensus of opinion is that it does not eradicate infection in most of the chronic cases. The drug is, however, worthy of trial and is especially suitable for private patients.

(d) **Aur-emetine** is a combination of periodide of emetine with the aniline dye auramine. It contains emetine 28 per cent., auramine 16 per cent. and iodine 56 per cent. It is a dark maroon coloured powder, insoluble in water. Aur-emetine was prepared by Martindale, and like emetine periodide is practically insoluble in the acid of the stomach. It is split up slowly by the alkali of the upper part of the intestine liberating emetine and auramine. Experiments with the drug showed that 20 per cent. was decomposed in four hours in physiological alkali at 40°C, but it is possible that decomposition is more rapid in the intestine as its administration is quickly followed by orange-coloured faeces. Brown (1926) using a suspension in gum found the growth of free-living amoebae inhibited to the same extent as with emetine and conessine under the same conditions.

In amoebic dysentery aur-emetine is said to be a further advance upon emetine periodide. The use of this drug is not attended with nausea, vomiting, abdominal pain or purging; it is also less depressing than

emetine. It is given in gelatine capsules in doses of one grain (0.06 gm.) four times a day after food on alternate days for seven days, and then daily up to a total of 40 to 60 grains. Stovarsol 4 grains a day on alternate days and rectal injections of 'emetol' may be combined with it, especially in chronic cases. When the liver is involved it is combined with injections of emetine. Given subcutaneously it is less depressing than emetine and therefore the patient need not be kept rigidly in bed.

(c) **Emetol** was introduced by Willmore and Martindale. It is a solution of emetine base, 1 grain (0.06 gm.) in 2 drachms (8 c.cm.) of olive oil and is used for rectal administration. Two drachms of this are added to 4 to 6 drachms (16 to 24 c.cm.) of ether and 8 ounces (230 c.cm.) of olive oil and this is injected slowly after a preliminary wash-out. The foot of the bed should be raised, as far as possible, during the injection. Injections are given every other day, five to twelve making a course. Beneficial results are claimed from the use of this drug, but it is difficult to administer and is not liked by the patients. The effect appears to be purely local. Probably a certain amount of emetine is absorbed when 'emetol' is given per rectum but the quantity cannot be large.

Par-emetol is a suspension of 1 grain of emetine in 2 drachms of liquid paraffin. This is given in 1 to 2 drachm doses at night with a drachm of sodium bicarbonate; the same precautions are taken as in the case of emetine-bismuth-iodide.

(f) **Arsemetine** is a solution of acetyl-amino-oxyphenyl-arsinate of emetine, a well defined chemical compound. One cubic centimetre of the solution contains 4 centigrams ($\frac{2}{3}$ grain) of hydrochloride of emetine and 0.92 centigrams ($13\frac{1}{4}$ grains) of arsenic. Physiological experiment shows that tolerance of emetine is enhanced by the presence of arsenic so that it is possible to administer larger doses. The dose is from 4 to 8 centigrams ($\frac{2}{3}$ to $1\frac{1}{4}$ grains) of emetine, that is to say, 1 to 2 c.cm. of Arsemetine.

(g) **Gavano**. Recently, another derivative of ipecacuanha has been prepared and introduced by Messrs. Bayer-Meister-Lucius under the name of Gavano. It is apparently a derivative of emetine (mono-methyl-esters of cephaeline) or cephaeline itself in combination with an organic acid, the nature of which is not disclosed. The drug is recommended to be given by the mouth in doses of 1 tablet thrice daily for 6 consecutive days or 1 tablet twice daily for nine consecutive days. It does not give rise to nausea and vomiting usually produced by emetine. The proportion of probable cures to the failures in the series of author's 18 cases was 1: 1.66.

Ravaut's Paste has the following composition: bismuth carbonate 100, wood charcoal 100, ipecacuanha 4 to 6, syrup 100, glycerine 100.

The dose is 2 to 10 table-spoonfuls given alternately with 0.1 gm. of nova-arsenobenzol for 10 to 20 days. It has no positive curative effect but possibly keeps in check the distressing symptoms.

Total alkaloids of ipecacuanha in amoebiasis. Roux (1923) employed subcutaneous injections of the total alkaloids of ipecacuanha with good results. In view of the fact that the amoebicidal action of emetine and cephaeline is about equal, the use of the total alkaloids of ipecacuanha in the treatment of amoebic dysentery is worthy of trial. The cost of treatment could be considerably reduced if the total alkaloids could be employed instead of the purified emetine.

In comparing the effects of the hydrochloride of emetine and of cephaeline on patients, Rogers came to the conclusion that though cephaeline hydrochloride both by itself and in combination with emetine, gave results far superior to the oral administration of ipecacuanha powder but judged from the general improvement in the condition of the patient and the disappearance of amoeba from the stools, it was distinctly inferior to an equal quantity of pure emetine hydrochloride. Cephaeline is more irritant and about twice as toxic and hence has never been widely employed.

Other uses of ipecacuanha and emetine. Ipecacuanha has been employed as an emetic and expectorant in the treatment of inflammatory conditions of the respiratory organs. For this purpose it is of course prescribed in very small quantities. Ipecacuanha increases the secretion of the bronchial mucous membrane. The increased secretion may be of service by protecting the inflamed and irritable surface of the mucous membrane from cold air and thereby lessening cough. The effects probably are purely reflex. It has also been employed as a diaphoretic. Emetine has been recommended for tuberculous hæmoptysis, but neither the clinical results nor its pharmacological action justify its use for any internal hæmorrhage; moreover some authorities believe it to be contra-indicated. Emetine has also been recommended in pyorrhæa alveolaris; it may produce improvement by destruction of *E. buccalis*, but it fails to cure this condition because this amoeba only occurs as a secondary infection and is not the cause of the disease.

Emetine has been used in the treatment of a number of other diseases. It has been unsuccessfully tried in syphilis, trypanosomiasis and bacillary dysentery. It has also proved useful in the treatment of metazoan diseases particularly in various types of schistosomiasis.

Acton advises injections of emetine in one grain doses in the treatment of leucoderma. He believes that in addition to its action on *E. histolytica* which is a common infection in these patients, the drug has a depressing action on the functions of the adrenals which are hyperactive in leucoderma.

Emetine in 1 grain doses has been given in sprue, but it produces no beneficial effects.

In pellagra it has been recommended when there is slight indication of buccal infection; 6 daily injections of $\frac{1}{4}$ grain (0.03 gm.) of emetine are given; after two weeks the course is repeated. If the mouth remains sore, four or five courses may be tried.

Emetine has been tried in *oriental sore*. Usually 20 minims of a 5 per cent. solution of emetine hydrochloride in distilled water are injected at the base of the sore round its thickened margins. Inflammation is set up and in 3 to 4 days the sore becomes a well-defined ulcer which is then treated on surgical lines. Emetine has no specific effect either in dermal or visceral leishmaniasis; the effect is purely a local irritant one.

CHAPTER V

TOXIC EFFECTS OF EMETINE

In adult human subjects the figures for immediate massive toxicity are not known. Fatal results however are to be feared with doses of 0.6 gm. and anything above a dose of 1.2 gm. is probably fatal at once. Eleven doses of 1.9 grains each would probably cause considerable damage in a man weighing 12 stone, while 35 doses of 0.8 grains each would be definitely risky. There should be long intervals (three months) between series of injections or courses to allow the drug to be excreted from the body.

No general disturbances or gastro-intestinal symptoms are produced in man when a therapeutic dose is given by injection; local reaction as a rule is small when the solution is neutral. Larger doses cause nausea, vomiting and diarrhoea. As much as 0.25 gm. has been given for a single dose without producing any other symptom except persistent nausea. But if a very large dose of emetine is given the patient may suddenly faint and death may occur from paralysis of the heart. In more slowly developing cases there is persistent nausea and vomiting, diarrhoea, vertigo, extreme muscular weakness and expiratory dyspnoea; the pulse is at first slow and then rapid. Death results from exhaustion, gastro-enteritis or intercurrent inflammation of the lungs. It should be remembered that there may be wide differences in the toxicity of various commercial samples of emetine.

Cumulative toxic effects of emetine. Those who have had experience of treating amebic dysentery cases are alive to the possibilities of the toxic action of this drug. Low in his series of cases, noticed diarrhoea secondarily arising during treatment with emetine and suggested that its unduly prolonged use in too high dosages might eventually produce symptoms of intoxication. It is however very difficult to determine by clinical observation alone, whether the local effects on the alimentary

canal and the general effects of toxæmia are to be attributed to emetine, or to the condition which had led to its administration. Dale and Dobell (1917) performed some very interesting experiments on healthy animals to elucidate this point. They used chiefly rabbits and cats and employed doses which in proportion to the weight of the animals would be regarded as rather too high for continued administration in man. The average weight of an adult man being taken as 65 kilograms, a dose of 1.0 mgm. per kilo. body weight is equal to about one grain for such a patient. Cats weighing 3 kilograms in these experiments were given doses of 5 mgm. which works out to $1\frac{1}{2}$ grains for an average man.

Such a dose given once only had no perceptible action of any kind on the animal and it could be repeated up to a point without any deleterious effects. If however the doses varying from 3-10 mgm. were continued for a fortnight, sooner or later symptoms of intoxication appeared and became rapidly intensified with persistence of the daily injections, leading to a fatal termination. In rabbits, a profuse diarrhoea attended with rapid emaciation was the prominent feature; in cats these symptoms were of secondary importance and sometimes were altogether absent, but lethargy and somnolence were marked and deepened to a terminal coma. The toxic effects consisted of pronounced gastro-enteritis, acute nephritis, œdema of the lungs, weakness and paralysis of muscles. Post-mortem examination showed damage to the liver and kidneys in addition to signs of intestinal irritation; the heart was pale and flabby. The results are very significant and clearly show the cumulative toxic effect of the drug in these animals. They demonstrate the serious danger of pushing emetine beyond a certain point and ought to serve as a warning against the indiscriminate and unguarded use of the drug.

Clinical experience has also established the fact that emetine is a cumulative poison in man. The dosage and the length of time during which it should be given have therefore to be very carefully considered. Formerly, untoward effects from its use were put down to the disease itself and this accounts for such diagnosis as post-dysenteric heart failure. Recent investigations

have shown that undoubted cases of sudden failure of the heart caused by emetine may occur. The depressing effect of the drug, if given in doses of one grain daily for some time, is very marked, the noticeable features occurring after 4th to 6th injections being loss of appetite, nausea, vomiting, abdominal pain and diarrhoea due to gastro-intestinal irritation. Among the serious symptoms of poisoning are an increased pulse rate, listlessness and cardiac depression. There may be general lassitude, disinclination to make an effort, weakness of the legs, tremors of muscles, globus hystericus, cardiac arrhythmia, low blood pressure and a feeling of faintness. General œdema, petechial hæmorrhages, purpuric skin rashes, hæmoptysis and signs of cerebral and pulmonary œdema may also be present. Albuminuria sometimes occurs. Polyneuritis is common and in some cases difficulty in swallowing and a feeling of constriction about the throat and chest have been noticed. Urticaria and large pruriginous plaques persisting for a month after the last injection have been known to occur even after a few injections. Sudden collapse and death may supervene in some cases. Auscultation of the heart in these cases shows similarity of sounds, and a lack of the muscular element in the first sound. Cardiac stimulants should be used at the earliest possible moment when the signs of cumulative toxic effects have appeared. Degenerative changes were noticed by Bais (1923) in human beings after prolonged use of the drug. Chopra and his collaborators (1924) demonstrated that in rabbits marked histological changes occur in the heart after emetine injections. These consist of cloudy swelling, disappearance of the traverse striations and atrophy and fibrosis of the muscle. The author (1934) has shown that degenerative changes are produced in the myocardium after therapeutic doses of emetine which can be detected by electro-cardiographic examination.

Emetine neuritis. Neuritis of the lower extremities is one of the early symptoms and is manifested at first by weakness in the legs, difficulty in walking and interference with the normal reflexes. Usually there is no pain on pressure as the motor nerve fibres only are affected. Wrist drop, ankle drop, toe drop, and hyperæsthesia of the soles of the feet, sluggish

knee jerks and loss of taste are noticed in some patients. It is possible that difficulty in swallowing and the sensations about the throat and chest produced after emetine injections are due to involvement of the nerves supplying those parts; it has also been suggested that these effects may be due to changes in the nuclei in the medulla oblongata similar to those that have been observed in the cells of the anterior horn of the spinal cord. In some individuals symptoms are produced after 8 or 9 grains of the alkaloid. Palsy may develop some considerable time after the cessation of treatment. Fibrotic changes in the nerve trunks have been noted after large doses of emetine in experimental animals, and similar changes probably occur in man.

Emetine has not been found in the cerebro-spinal fluid, but it causes a slowly-advancing paralysis of the central nervous system in frogs. There is experimental as well as clinical evidence to show that peripheral neuritis is produced very early after a course of emetine injections. Emetine does not affect the nerve fibres indiscriminately but has a predilection for those conducting motor impulses. The weakness in the legs seen after emetine administration may also be due to damage of the muscle protoplasm.

Emetine diarrhœa. Emetine when given in considerable quantities produces diarrhœa. It has already been pointed out that in animals emetine may produce gastro-enteritis with hæmorrhages in lymphatic glands, spleen, kidneys and thymus. These experimental animals die even though emetine is discontinued directly the symptoms appear. Diarrhœa which is the first sign of irritation of the gastrointestinal tract was quite common in the old days, the rationale of ipecacuanha treatment being to push the remedy till profuse diarrhœa was produced and the stools became liquid and of a canary yellow colour. After discontinuing the drug the stool assumed its normal consistency and to all intents and purposes the patient was considered cured. Whether the cure was real or not is uncertain as in those days cysts were not recognised. Low (1915) noticed that diarrhœa (occasionally with blood) occurred after hypodermic injections

but not so commonly as when ipecacuanha was given by the mouth. It is not unusual for the patient to get a slight attack of diarrhoea after the sixth injection. Since the oral administration of emetine-bismuth-iodide has come into vogue, diarrhoea has become more common, and when mild this is considered to have a beneficial effect and is not a sign of intoxication. In addition to the specific action of the drug, the bowel is at the same time thoroughly washed out and this mechanical process is valuable as is evident from the successful treatment of bacillary dysentery with saline purgatives. A few days after the termination of the course (3 grains of double iodide for 12 successive days) the stools commence to become solid and in successful cases gradually assume normal consistency.

Cautions and contraindications. Emetine is a protoplasmic poison acting equally on all tissues, heart failure being the actual cause of death. In cases where the heart or kidney is affected, it is advisable to give as small doses as possible for the treatment of dysentery. In otherwise healthy individuals the number of injections should be limited as far as possible, and under no circumstances should more than one grain be given in 24 hours.

Emetine, if administered continuously for therapeutic purposes, depresses the heart, but signs of cardiac depression improve when it is withdrawn. Caution is indicated in all cases where the myocardium is damaged by other diseases such as malaria (malignant form), influenza, diphtheria, etc. It is advisable that the patient should remain in bed during the period of emetine treatment and an accurate record of the pulse rate should be kept. If this is definitely increased, or palpitations occur, the drug should be withheld till the heart resumes its normal rate.

Convalescents who have received a course of emetine should be allowed to leave the bed very cautiously so that the effects of the drug pass off and if the pulse rate goes up, they should return to bed. The author has seen patients whose hearts were permanently strained for want of this precaution. Emetine is a powerful drug and appears to have a selective action on the heart muscle.

Emetine in pregnancy. It has been suggested that emetine should be avoided in pregnancy as it may cause abortion. Some pharmacologists have stated that emetine increases the contractions of the uterus and have issued a warning against its use in pregnancy. On the other hand clinicians have given injections of emetine in advanced cases of pregnancy without untoward results. Recent investigations have shown that after a dose of one grain, assuming that the whole of the alkaloid is absorbed, the concentration of the drug in the blood cannot possibly be greater than 1 in 150,000 to 1 in 100,000. Such dilutions have little effect on the isolated uterus, and if there is any action at all, it is a tendency to relaxation. Acton and Chopra (1923) showed that abortion is more common in cases of bacillary dysentery and is produced by the bacterial toxins; they showed that the toxin of *B. dysenteriae Shiga* is a powerful ecboic. Emetine does not appear to be a causative factor in producing abortion and the coincidence of a miscarriage when injections are being given seems to be due to the toxins of the parasite rather than to the drug. Pregnancy is not therefore a contra-indication to the use of emetine. In menstruating women it is preferable to start the injections after the period is over but in urgent cases treatment should not be deferred.

CHAPTER VI

MODE OF ACTION OF EMETINE

The manner in which emetine acts in amœbiasis has lately been the subject of much discussion. Vedder's observations that emetine hydrochloride in dilution of 1 in 100,000 inhibited the movements of *E. histolytica* were not confirmed by Dale and Dobell (1917). Quinine was found to be more toxic to the entamœba *in vitro*, yet it had not the slightest effect when administered in amœbic dysentery in large doses, whereas emetine was effective in very small doses.

Dobell and Laidlaw (1926) showed that the conclusions regarding the action of emetine on *E. histolytica* had been based on the results of imperfect technique. It was shown that the time of survival of the entamœba outside the body is short and thus the organism can only be given slight exposure to emetine. These results were compared with the therapeutic effects, where the action of emetine on the amœbæ was spread over many days and this was the cause of the disagreement. They devised a technique by which the entamœbæ could be grown on a liquid medium and the action of different concentrations of the alkaloid was observed on the culture which was kept in an incubator for prolonged periods. With this technique quinine concentrations lower than 1 in 1,000 gave cultures of *E. histolytica* as rich as the control. Stovarsol had no effect in dilutions of 1 in 20,000 or less. *E. histolytica* was very susceptible to emetine. In simple liquid medium 1 in 5,000,000 of emetine hydrochloride was lethal for *E. histolytica in vitro* within four days, provided the pH of the medium was about 6.4. With greater acidity of the medium the effect of emetine was much reduced. *E. coli* growing in the liquid medium were killed in dilutions between 1 in 300,000 to 1 in 600,000 with a pH of 6.8 to 7.8. In mixed infections of *E. histolytica* and *E. coli*, emetine eradicates the former leaving the latter free. These experiments demonstrate that the dose of emetine or other alkaloids required to kill *E. histolytica* immediately bears no relation to the minimum dose of the same alkaloid which is eventually lethal, if maintained for some time. A very small quantity of emetine, if constantly present in the intestines for days or weeks, would probably suffice to make life therein impossible for *E. histolytica* though not for *E. coli*. The important conclusion which can be drawn from these experiments is that emetine has a weak amœbicidal action on *E. histolytica* and cures amœbic dysentery by

direct destruction of these organisms. The point worthy of notice is that in order to eradicate the infection, one must aim at maintaining continuously over as long a period as is safe, a sufficiently high concentration to kill the amoebæ. As regards the failure of emetine to kill entamoebæ in the cat, it has been suggested that man and the cat may deal with emetine in different ways. In the cat most of the emetine is rapidly excreted in the urine and not in the gastro-intestinal tract. Some human beings infected with *E. histolytica* appear not to react to emetine treatment. This is not due to emetine-resistant strains, but possibly to the excretion of the alkaloid in larger quantities by the kidneys than by the gastro-intestinal tract.

The other important factor lies in the tissues of the host, and we have to find out if any change takes place in these so as to make it impossible for an obligatory tissue parasite such as *E. histolytica* to penetrate the tissues and obtain the only food on which it can thrive and multiply. It is said that entamoebæ do not touch emetinised red blood corpuscles. Is it possible that the presence of emetine in the tissues of the host prevents this parasite from making use of them for its food? Or is it more likely that the presence of minute quantities of emetine prevents the entamoeba by affecting its mobility or some other function from penetrating into the tissues or using them as food, and thus it dies of starvation?

Be that as it may, there is no doubt that when we attempt to exterminate the protozoal parasites from the body, the administration of a drug like emetine destroys a large majority of these parasites. The body resistance then rises and the patient's own power of resistance finally exterminate the residual parasites. This undoubtedly occurs in kala-azar and appears to hold good for malaria, trypanosomiasis and amoebiasis as well. Two factors, therefore, appear to be concerned in recovery, (1) the natural resistance of the host and his tissues, (2) the moderate amoebicidal action of the drug. A lowering of either of these allows the disease to progress.

CHAPTER VII

OTHER AMŒBICIDAL REMEDIES

HOLARRHENA ANTIDYSENTERICA

It is a small deciduous plant belonging to the natural order Apocyanaceæ. It is also known by the name of *H. codaga*, *H. pubescens*, *H. malaccensis*, *Wrightia antidysenterica*, and *Chenomorpha antidysenterica*. Two species *H. congolensis* and *H. wulfsbergii* growing in West Africa also have a reputation in the treatment of dysentery. In England it is known as bitter oleander, dysentery rosebay, oval-leaved rosebay or conessi bark tree. In Sanskrit it is called *Indrayav* or Indra's seeds, *Kutaja* and *Kulinga*; in Hindi, it is known as *Indrayaba*, *Kureya* and *Dubhi*; in Bengali, *Kurchi* or *Kutrai*; in Persian, *Indrajavatalkh*.

The plant is widely distributed throughout the plains of India and Burma in deciduous forests and open waste land, where it is often gregarious. It grows in the valleys of the outer Himalayas up to a height of 4,000 feet above the sea-level, and is abundant in the sub-Himalayan regions. It is also common throughout the greater part of the Indian peninsula down to Malabar and Travancore and grows abundantly in the forests of Burma. *H. antidysenterica* is often mistaken for another species of the same family, viz., *Wrightia tinctoria*, in fact Linnaeus was originally responsible for this confusion. In 1809 Brown revised the whole of the family of Apocyanaceæ and rectified the mistake. In spite of this the two plants have been mistaken for each other. *Wrightia tinctoria* is inert and it is largely owing to this fact that *H. antidysenterica* did not attract much attention, because more often than not the inert bark was used instead of the active Holarrhena. The tree flowers in April to June or sometimes July to August; the fruits are full-sized from August to October and ripen from February to April. The flowers are like those of white jasmine and have a fragrant odour.

Both the bark and seeds of this plant are among the most important medicines of the Hindu materia medica; infusions made from these have been used in the treatment of dysentery for many centuries. The Hindu physicians consider the plant to have bitter, stimulant, antipyretic, astringent and antidyenteric properties. It stops hæmorrhage, is an expectorant and is used as a tonic. It forms part of many preparations in the Ayurvedic (Hindu)

and Tibbi (Mohammedan) medicine. Kanai Lall Dey (1896) was so struck with its therapeutic value that he advocated that it should be included in the British Pharmacopœia.

Chemistry. *Seeds.* The seeds contain 29.36 per cent. of a fixed oil and 0.025 per cent. of the alkaloids.

Bark. As early as 1858 Haines isolated an alkaloid which he called *nericine* from the Linnæan name of the plant, *Nerium antidysentericum*. In 1864 Stenhouse isolated an alkaloid from the seeds which he called *wrightine* after the then commonly accepted name *Wrightia antidysenterica*. Both these names were rejected in 1865 by Haines who called the alkaloid *conessine*. Ranchandra Dutt (1880) gave the name of *kurchicine* to the alkaloid after its Bengali name. The same alkaloid occurs in the two African species mentioned above and Pyman (1919) isolated a new alkaloid to which he gave the name of *Holarrhenine*. Ghosh and his collaborators (1928) found in the Indian variety a second alkaloid in addition to conessine differing from holarrhenine which they named *kurchicine*, and a third alkaloid with a low melting point named *kurchine*. Assay of the powdered bark shows that it contains 1.5 per cent. of total alkaloids by weight; but it is difficult to get conessine in pure condition out of the crude total alkaloids, much being lost in the process of purification. Besides these alkaloids a number of tannins are present in the root.

Pharmacological action. The Pharmacological action of conessine was studied first by Keidel (1878) who found that this alkaloid depressed the centres for conscious sensation and voluntary movements in the brain. The activity of the vasomotor centre was depressed and the reflexes tended to disappear. The alkaloid also increased the peristaltic movements of the intestines and induced contractions of the bladder. Keidel concluded that the action of conessine resembles that of morphine. Warnecke (1888) found that the alkaloid was excreted in the urine of dogs as dioxy-conessine. Burn (1914) stated that both conessine and holarrhenine have a similar physiological action. They both produce a considerable narcotic action in the frog but this action is inappreciable in mammals. They also possess a marked anesthetic action on the cornea. Both the alkaloids produce local necrosis when injected subcutaneously. Both conessine and holarrhenine delay the conduction in the auriculo-ventricular bundle producing inco-ordination and heart-block. The isolated heart of a rabbit comes to a standstill halfway between systole and diastole. In small doses intravenous injections of both alkaloids produce a rise of blood pressure. This rise is still present when the vasomotor nerves are paralysed, so it must be due to the direct action of the alkaloids on the muscles of the arterioles. According to Giemsa and Halberkahn (1918) large doses can be given to man without producing necrosis. Brown (1922) appears to have been the first worker to test the power of conessine, the chief alkaloid of *kurchi*, as an amoebicide. Working with cultures of pond amoebæ

he found conessine to be distinctly lethal and that when it was incorporated with the culture-medium in a strength of 1 in 1,000,000, it inhibited their growth. Experiments with mice showed it to be much less toxic than emetine but subcutaneous administration in medicinal doses, according to him, produced local necrosis. On the other hand, he found that it can be safely given by the mouth in large doses. Henry and Brown (1923) on testing the tannins of kurchi bark and of ipecacuanha against the free-living ciliate protozoon, *Glaucoma*, found both to be highly toxic to this organism. The alkaloids have little or no effect on the bacilli of the dysentery group.

The pharmacological action of conessine has been fully studied by Chopra and his co-workers (1927). It was found to be lethal to *Paramœcium caudatum* in a dilution of 1 in 2,800 of its molecular weight, and in a dilution of M/20,000 in the presence of N/200 NaOH. It killed free-living amœbæ in a dilution of M/1,000 and in a dilution of 1 in 280,000 in the presence of N/200 NaOH. Its action on the vegetative forms of *Entamœba histolytica* was tested on the dysenteric stools of experimentally infected kittens. In mucus flakes in such stools it paralysed the motile amœbæ, in dilutions of 1 in 230,000 in 8 minutes in the presence of an alkali, and in 18 minutes in the absence of alkali. Emetine in dilutions of 1 in 200,000 was found to be ineffective against the amœbæ, but paralysed them if alkali was present. Conessine had but little action upon *Trichomonas hominis*, but was markedly lethal to the coprozoic flagellate protozoon, *Bodo caudatus*. Conessine salts can be given subcutaneously and intramuscularly. Contrary to what was reported by Brown, these workers found that no necrosis of the tissues followed its hypodermic injection. Intramuscular and subcutaneous injections of conessine hydrochloride produce less local reaction and pain than emetine.

The statement of Burns on the action of conessine on the heart muscle, if it were true for the total alkaloids, would make one hesitate to administer them in large doses. Any limitation in the dosage would defeat the end in view which is to attain a concentration of these alkaloids in the large intestine sufficient to kill the *E. histolytica* in spite of the acidity that is present in the gut contents or in the surface tissues. The author and his co-workers therefore investigated the action of these alkaloids in detail.

(a) *Gastro-intestinal tract.* These alkaloids have an inhibitory action on the activity of the digestive ferments such as ptyalin, pepsin and trypsin. The peristaltic movements of the intestines are inhibited. The alkaloids have no emetic action and do not produce nausea.

(b) *On the circulation.* Small doses, 2 mgm. injected intravenously into the saphenous vein of a cat weighing 2 kilo., caused a persistent fall of blood pressure, but without any alteration in the intensity or frequency of the heart beat. In much larger doses,

there was slowing of the heart beat. Perfusion experiments with the isolated heart rarely showed any effect on the frequency or force of the contraction. Doses of 2 to 5 mgm. in a cat of 2 kilo. showed no alteration in the auricular and ventricular contractions as seen in myocardiographic tracings. Although there is a marked rise in pulmonary pressure with conessine and kurchicine, the rise is only slight when the total alkaloids are injected into the animal. The fall in blood pressure is not due to a direct action on the heart or heart muscle.

(c) *The volume of various organs and structures in the body.* The limb volume and that of the liver, spleen and kidney were all decreased after intravenous injections of the total alkaloids, indicating that vaso-constriction was occurring at these sites. On the other hand, there was a very marked increase in the intestinal volume with complete inhibition of intestinal movements; this was recovered from after a few minutes.

(d) *Local effects of intramuscular or subcutaneous injection.* When a 6 per cent. solution was injected into the tissues no hæmorrhage or necrosis was observed, but a good deal of œdema occurred at the site of injection. The œdema was most marked in 24 hours and disappeared completely in 48 hours after the injection; hyperæmia and œdema were due to the acidity of the salt of the alkaloids. One to two grains of the total alkaloids give rise to no signs of hæmorrhage or necrosis such as is seen with emetine or quinine.

(e) *Uterus.* The total alkaloids have very little effect on the excised uterus or on the uterus *in situ* except in strong concentrations which it is impossible to attain in the circulating blood. The alkaloid *kurchine* with a low melting point is the most powerful, causing contractions in a concentration of 1 in 50,000. Most alkaloids circulate in the blood at a concentration of 1 in 500,000 to 1 in 150,000. Therefore these alkaloids would have no effect on a pregnant uterus.

(f) *Excretion.* The alkaloids are mainly excreted by the gastrointestinal tract and by the kidneys. They can be detected in the urine soon after intramuscular or oral administration. The excretion goes on for nearly a week after cessation of the treatment.

The action of low-melting point alkaloids has been worked out by Chopra and his co-workers (1933) and is very similar to conessine.

There is no emetic or depressant effect in man when 20 grains of the bismuthous iodide salt of the total alkaloids are given daily for 10 days. The pulse remains normal in frequency, tension and rhythm. There is no alteration in the heart sounds, even in a case of cardiac disease. The drug does not cause irritation of the alimentary canal like emetine. If it does occur,

this is probably due to a co-existing infection with *B. dysenterica* (Flexner or Strong).

Therapeutic uses. The bark and seeds of *H. antidysenterica* have been used in the treatment of dysenteries of India for many centuries. It appears to be used in the indigenous systems in two forms:—

(1) As kurchi bark, either in the form of a powder or watery extract.

(2) As *India Jav*, an emulsion of seeds. Tull Walsh (1891) refers to the use of the bark as being approximately equal in its effects to emetine mercuric iodide. The drug, however, was not tried properly in the treatment of dysentery until lately. Tablets made from the powdered bark have been put on the market by Barroughs Wellcome & Co., and have been combined with emetine injections. Drake-Brockman (1926) used this drug as an adjuvant to emetine in the treatment of chronic amoebic dysentery with excellent results. Different preparations of the drug have been tried in the treatment of amoebic dysentery.

The drug is now used in one of the following forms.

(1) *Bark*. Sixty grains of the bark in the form of tablets of 1 to 2 drachms of the extract are given orally every day for ten days. The improvement is less rapid than with emetine but seem to be more lasting. These findings are in accord with those of Tull Walsh in 1891. The ratio of probable cures to failures by this treatment in a series of 16 cases was 1 : 1.

Emetine may be combined with *H. antidysenterica* bark. The latter may be given either in the form of powder or extract together with a course of emetine injections. In a series of 9 cases the ratio of probable cures to failures worked out to be 1 : 1.

(2) *Conessine*. One to two grains of conessine are given intramuscularly every day for 10 consecutive days. The drug is well tolerated but the results are not so good as when the powdered bark or the extract is given. Henry and Brown (1923) found the tannins of *H. antidysenterica* bark highly toxic to free-living protozoa and it is possible that the superior action of the powdered bark and the extract is probably due to the presence of these compounds. The ratio of probable cures to failures in a series of 9 patients treated by this method was 1 : 2.

(3) *Total alkaloids*. Injections of total alkaloids have been tried in a number of cases. In uncomplicated acute cases of amoebic dysentery the vegetative forms of entamoebæ disappear rapidly from the stools and as a rule do not reappear. In cases with co-existing bacillary dysentery and in chronic forms of amoebiasis the results are less favourable. Total alkaloids have also been given by the mouth; they do not produce nausea or vomiting.

(4) *Kurchi-bismuthous-iodide*. Acton and Chopra (1929) prepared bismuthous iodide of the total alkaloids of kurchi which they called 'kurchi-bismuthous-iodide'. This double salt is insoluble and can reach the large intestine in sufficient concentration to kill the entamoebæ, if large enough doses are given. The drug can be tolerated in doses of 10 grains twice daily, there being no appreciable effect on the heart or blood pressure, no depressant or emetic effect and no irritation of the gastro-intestinal tract such as are observed in the case of emetine.

The author at first tried the effect of injections of the total alkaloids in 10 cases of amoebic dysentery some of which were acute and others chronic. The drug was given in doses of one grain daily intramuscularly; a marked local reaction was however produced. In this series there was one failure. In another series of 20 cases kurchi-bismuthous-iodide was given twice daily in doses of 4 grains curing 12 cases. Two required a second course; of these one was cured.

It will thus be seen that in acute cases of amoebic dysentery kurchi alkaloids are as powerful as emetine in their immediate effect on the symptoms as well as in their curative value, even in one grain doses. No toxic effects were noticed even with injections of two grains daily except flushing of the face immediately after the injection, but this did not last for more than a few minutes. Some patients complained that they could not sleep after injection of such large doses. The injections were however very painful and had to be given up.

The cause of failure in treatment both with emetine and the kurchi alkaloids is due to secondary bacterial infection of these ulcers by streptococci, *B. dysenteriae* (Flexner), or *Bact. pseudo-carolinus*, etc. These organisms form a large amount of acid from the carbohydrates, which diffuse into the tissues from the gut and also into the gut contents. These alkaloids are ten times more powerful when acting in a substrate at a pH of 8 than when acting at a pH of 6. There are three methods of overcoming this acidity of the gut contents. The first method, and one that seems the most obvious, is to administer large doses of alkalis by the mouth, *e.g.*, one to 2 drachms of bismuth carbonate every 2 to 4 hours, sodium bicarbonate or potassium citrate. These drugs have very little effect in reducing the acidity of the large intestine. Clinical-

ly this method is useless. The second method is to deal with the organisms that are responsible for the production of this acidity by isolating them, preparing a vaccine, and then immunising these patients against their own organisms. In this way it has been possible to alter the pH of the stool from 6.8 to a pH of 7.35 after three weeks of immunisation. That this method is a sound one is shown by Acton and Chopra (1929); even in spite of repeated failures with emetine, cure can be effected by combined treatment with vaccines and emetine. More recently Acton and Chopra (1933) by using the bismuthous iodide compound of the total alkaloids of Kurchi in doses of 10 grains (0.6 gm.) twice daily for 10 to 20 days, preceded half an hour before by a mixture containing one drachm of sodium bicarbonate and 40 grains (2.6 gm.) of sodium citrate, obtained a proportion of probable cures to failures of 3.16 : 1 in a series of 78 cases. In obstinate and persistent cases, a prolonged course (1 to 3 months) of standardized extract of kurchi, 1 to 2 drachms twice daily, with or without *plantago ovata* (Isabgul) is often effective.

The third method is to give the drug in large doses in order to attain a sufficiently high concentration to be effective in an acid substrate. Fortunately, the total alkaloids of kurchi bark are not toxic, so that large doses can be given, and we can also form an insoluble bismuthous iodide compound, which will not begin to act until it reaches the acid substrate in the cæcum and large intestine. This actually does occur, as qualitatively it is found that the kurchi alkaloids appear in the urine of patients taking the bismuthous iodide compound. *Entamoeba histolytica* may be living in the tissues or in the lumen of the gut. In the former case, it will be in contact with the serum and body fluids at a pH of 7.2, whilst in the gut the contents may reach a high degree of acidity between a pH of 5 and 6.

It is necessary to explain the somewhat discordant results obtained by different clinicians in the treatment of chronic intestinal amoebiasis with kurchi-bismuthous-iodide. The process of preparation materially alters the alkaloidal content and uniform results are always obtained if the compound is prepared according to the method laid down. In some

cases of failure it was discovered on investigation that the process of manufacture described had been modified, and in order to facilitate the extraction of the alkaloids, hot alcohol had been used instead of the cold as originally recommended. This had the effect of changing the alkaloids, and possibly radical changes were produced in the one with a low melting point which forms the chief constituent. The failures are also to be attributed to the fact that the supply of good fully-matured bark sometimes cannot keep pace with the large demand and consequently large quantities of immature, improperly collected and imperfectly dried bark come into the market. Such barks are sometimes employed for the extraction of the alkaloids used in the preparation of kurchi-bismuthous-iodide. The discordant results so far as kurchi-bismuthous-iodide is concerned, are due to:—

1. Some fault in the procedure of extraction of the alkaloids from the bark or preparation of the compound.
2. The bark from which the alkaloids are extracted not being mature, being improperly collected or being imperfectly dried.

Kurchi-bismuthous-iodide was originally prepared in the Calcutta School of Tropical Medicine on the same lines as emetine-bismuth-iodide by the cold extraction process. Its approximate composition is as follows:—Total alkaloids 27 per cent., bismuth 22.85 per cent., and iodine 50.15 per cent. The dose is 10 gr. twice daily preceded half an hour by an alkaline mixture. In simple cases a course of 10 days' duration is given; when mixed infection exists 15 to 20 days may be necessary.

YATREN

Synonyms:—Loretin, quinoxyl, 'Yatren 105' was prepared by Behring & Co., and is claimed to be 7-iodo-8-hydroxyquinoline-5-sulphonic acid. It is a finely crystalline powder, pale yellow in colour; it easily absorbs moisture, and must therefore be kept dry. It has 36.2 per cent. of sodium carbonate added to increase its solubility. It has no odour, has a solubility of 4 to 5 per cent. in water. When dissolved it is said to become iodine-oxyquinoline sulphate of sodium with the liberation of carbon dioxide. Yatren is said to be almost as good a specific for amebic dysentery as quinine is for malaria but this claim has not been substantiated. In Japan a brand of locally prepared iodine oxyquinoline sulphate of sodium has been used with success in the treatment of both forms of dysentery; it is considerably cheaper than 'yatren 105'.

Pharmacological action. Yatren is claimed to be a cell stimulant and a strong disinfectant. The action of yatren on cultures of *E. histolytica* 'in vitro' has been studied. A solution of 1 in 100 kills amœbæ in a few hours; solutions of 1 in 4,000 to 1 in 5,000 inhibit multiplication and the cultures generally die out. The amœbæ prove resistant to the action of 1 in 10,000 concentrations. Taken by the mouth Yatren is a gastro-intestinal irritant and produces diarrhoea even in small doses. Given intravenously in animals, a 5 per cent. solution produced no fall of blood pressure or other untoward effects. Yatren is readily absorbed from the small intestine and from the rectum; it is excreted in the urine which gives a positive oxyquinoline test, i.e., green colour with ferric chloride. Iodism is never produced though yatren contains 36 per cent of iodine.

Use in amœbic dysentery. Although it can be injected either intravenously or intramuscularly it is generally given by the mouth or as an enema. When given orally it is made up into pills of 4 grains (0.25 gm.) or in cachets containing 8 grains (0.5 gm.). A total of 15 to 22 grains (1.0 to 1.5 gm.) per day can be given. The drug is given daily for a week and repeated for 2 or 3 days during the following two weeks; when given as an enema, a 2 per cent. solution should be used and about 200 c.cm. is given slowly and retained as long as possible. This suffices in acute cases. In resistant cases the drug should be given by the mouth as well as by enema which should be given at night and retained all night if possible.

Muhlens and Menk (1921) were the first to use yatren in 8 resistant cases with remarkable clinical improvement. They gave it by the mouth in the form of keratin-coated pills in doses of 1 gm. three times a day, and supplemented it with rectal injections of 2.5 per cent. solution when ulceration was present. The first course consisted of combined oral and rectal use for 8 to 14 days with sigmoidoscopic controls. A further course of 3 to 7 days was given after a week's interval and later one more if necessary. Birt (1923) tried it in a series of 28 cases of which 16 were believed to be cured. He used enemata of 10 gm. of yatren in 100 c.cm. of water but patients complained of considerable pain. Huppenbauer (1925) claimed that the value of yatren lay in its efficacy in the treatment of chronic amœbiasis and its complications when emetine and emetine-bismuth-iodide had failed. Katsurada (1926) stated that his experience with

yatren had been very satisfactory. He only gave 1.8 gm. daily for 7 days after which the stools became negative. Hirayama (1925) treated 713 cases successfully. Boyers (1925) states that complete eradication of both motile and encysted *E. histolytica* with this drug was problematical. It is however a valuable adjunct in the treatment of this disease. According to Akashi (1926) yatren kills the entamoebæ present in the lumen of the intestine and then gradually attacks those in the superficial layers of the intestinal wall. Emetine, on the other hand, does not act on the amoebæ in the lumen of the gut, but kills the large forms in the intestinal tissues. He therefore recommended that the two drugs should be combined, but considered it advisable to treat acute cases at first with emetine till symptoms abate. Bach and Steinhauer (1926) observed rapid and complete restoration to health with this drug in chronic cases of amoebic dysentery. Dalmeyer (1926) working in Java found yatren unfailingly successful, both in acute and chronic amoebic dysentery. According to Deutsch (1927) yatren is practically a specific against all forms of dysentery in children. Manson-Bahr and Sayer (1927) obtained excellent results.

Yatren has been tried in the Carmichael Hospital for Tropical Diseases, Calcutta, by Megaw, Knowles and others with variable results. Such large doses as have been recommended by the makers and various investigators cannot be given without producing severe diarrhoea. Any dose above 15 to 30 grains (1 to 2 gm.) per day is liable to produce diarrhoea immediately and although there is no tenesmus present, it is troublesome to the patient. Knowles (1928) found that unless diarrhoea is produced the results of treatment appear to be poor. In fact the drug seems to act by producing irritation of the mucous membrane of the gastro-intestinal tract especially of the colon. In a series of 23 cases treated orally yatren gave a ratio of probable cures to failures as 1: 1.3. In 6 intractable cases of chronic dysentery which had combined treatment with yatren by the mouth and per rectum simultaneously, the ratio of probable cures to failures was 1: 1.5.

As may be expected certain cases respond much better to treatment by yatren than others. In chronic cases combined

treatment, *i.e.*, yatren by the mouth and per rectum is advisable. The chief disadvantage of this treatment is the high cost. A standard course of 8 pills orally per day for ten days with a daily rectal injection of 200 c.cm. of 2.5 per cent. solution will cost nearly 20 rupees or approximately 30 shillings. Moreover, this form of treatment is troublesome to the patient and very few can be persuaded to continue with rectal injections for more than a few days. It can only be carried out properly in nursing homes and in large hospitals. Some clinicians have given the drug by intravenous injections but the results have not been superior to those by the other routes. Yatren has also been advised in cases of amœbic hepatitis or even liver abscess, and patients suffering from bacillary dysentery are said to derive benefit from it.

From a perusal of reports of different investigators it is obvious that yatren is worthy of trial in the treatment of chronic cases of amœbic dysentery or carriers, in combination with emetine injections or emetine-bismuth-iodide by the mouth. It has been abundantly demonstrated that both these drugs possess a definitely curative value in amœbiasis, which may be limited when they are used singly. Yatren is readily absorbed but it is possible that it may not reach all the lesions in the bowels in sufficient concentration to kill the parasites. Its action may be intensified when it is combined with emetine by injections. The combination is well tolerated and gives very satisfactory results.

Preparations.

Yatren or sodium iodo-hydroxy-quinoline sulphonate. Dose up to 15 grains (1.0 gm.) daily. *Chardyl* is a Belgian preparation comparable to yatren.

Emetron is a yatren emetine compound which has been introduced for intramuscular injections but is not very effective.

Yarten-casein ampoules for intramuscular and intravenous use have been prepared.

Bismutho-yatren A. & B. have been introduced and tried in the treatment of yaws. The A. compound is the sodium salt of bismuthyl-iodo-oxyquinoline sulphonic acid containing the equivalent of 10 mgm. of bismuth metal per c.cm. The B. compound differs only in being a quinine combination in oily suspension containing 38 mem. of metallic bismuth per c.cm. A. can be used intravenously or intramuscularly, B. intramuscularly only.

Halogenated oxyquinolines. Owing to the relatively non-toxic and supposedly efficient amœbicidal properties of yatren or iodo-oxyquinoline sulphionate, a number of related compounds have been introduced. One of these higher halogenated oxyquinolines, iodo-chloroxyquinoline (vioform, N. N. R.) gives promise of success and is considered better than Chiniofon (N. N. R.) which is sodium iodoxyquinoline sulphionate. This compound is rapidly excreted in the urine in human beings, is non-irritating when given in capsules by the mouth, and no untoward symptoms from its continued administration (250 mgm thrice daily for two days) have occurred in amœbiasis. It appears to be more effective against *E. histolytica* than against other intestinal protozoa.

Anayodin. (Iodoxyquinoline sulphonic acid) has been tried in acute and chronic amœbic dysentery with good results.

ORGANIC ARSENICALS

Stimulated by the success obtained after the oral use of stovarsol (3-acetyl-amino-4-hydroxy-phenyl-arsonic acid or acetarsone, N. N. R.) in syphilis by Fournau (1921), Marchoux (1923) first employed organic arsenicals by the mouth in the treatment of amœbiasis. He found stovarsol to be effective and since then this drug has enjoyed some popularity as an amœbicidal agent. No special chemotherapeutic studies in this connection appear to have been made except that a related compound treparsol (3-formylamino-4-hydroxyphenyl arsonic acid) was tried. Two types of organic arsenicals have been studied in comparison with stovarsol. One series represent carbarsone (4-carbamino-phenyl arsonic acid) and tryparsamide, and the other consists of a series of arsenious trithio compounds represented by arsenious trithio salicylic acid. These compounds are cumulatively toxic but apparently quite active. Of the p-amino-arsonic acid series, the propionamide and the butyramides are not readily available and tryparsamide is not sufficiently effective. Thio-carbamino-phenyl arsonic acid differs from carbarsone only in that an atom of sulphur replaces an atom of oxygen in the carbamino radicle. This replacement makes the compound much less toxic and amœbicidal.

Stovarsol has been used in those cases who had resisted emetine treatment, in doses of 0.25 gm. in pill form twice daily for a period of 10 days. Amœbæ or cysts were found in the stool even after the treatment. Petzetakis (1925) tried the drug exten-

sively and found it an excellent remedy for parasitic infections of the intestinal tract; in infants doses recommended up to one year of age are 0.05 to 0.08 gm. daily; from 1 to 2 years, 0.08 to 0.10 gm.; from 2 to 5 years 0.10 to 0.25 gm. daily. In chronic and relapsing cases of amœbiasis prolonged treatment is necessary and may be supplemented by injections of emetine. He found that the drug can be exhibited over a prolonged period without producing any ill effects. To avoid toxic symptoms, which frequently occur with the drug, the dose should not exceed two tablets (8 gr.) daily for 7 days or 1 tablet (4 gr.) daily for 14 days. Brown (1926) considers that stovarsol is more effective in eradicating amœbæ than emetine. Van Steenis (1927) found stovarsol less effective than emetine or yatren, but very useful against the 'minuta' type of *E. histolytica*.

Knowles (1928) in summing up the literature on stovarsol, says that it is apparent from the large series of papers that on the whole the results are not too bad. Almost every writer comments on the drug as one easy to administer and well-tolerated by the patient. On the other hand it has less powerful amœbicidal action than emetine, and some authors comment on its toxic effects. Occurrence of a measles-like rash was not uncommonly met with and cases of acute exfoliative dermatitis have been recorded after administration of stovarsol. Knowles treated 32 patients, mostly chronic, in Calcutta; the ratio of probable cures to failures in these was 1: 1.1. He is of opinion that stovarsol has a definite place in the treatment of chronic intestinal amœbiasis. The ease and simplicity of the treatment are remarkable. The usual course is one tablet of 4 grains each night and morning for ten days. No toxic symptoms were observed, while the drug undoubtedly has a hæmatinic value. The patients taking stovarsol are not the miserable and unhappy beings like those on emetine or emetine-bismuth-iodide treatment. The average cost of treatment is 2 to 3 rupees. It is particularly useful in chronic type of cases and the chances of eradication of the infection are 40 to 50 per cent. The drug was used by Knowles as an after-treatment, the relief of clinical symptoms being first obtained with emetine injections and bismuth treatment. The patient was then given a few days' rest

and a ten-day-course of stovarsol afterwards. This usually leads to rapid improvement in general health and the infection may be eradicated. For chronic carriers stovarsol may be followed by a course of emetine-bismuth-iodide.

Carbarsone. This compound 4-carbamino-phenyl arsenic acid was first prepared by Ehrlich in 1909 and is a white crystalline powder, stable in air, without odour or taste. It contains 28.85 per cent. of arsenic when anhydrous. It is practically insoluble in water but dissolves in alkaline aqueous solution, and it melts at 174°C. Carbarsone has been put on the market by Eli Lilly & Co., of Indianapolis, U.S.A., and is available in capsules of 0.25 gm. each; recently the drug has also been manufactured by an Indian concern. Carbarsone is absorbed on oral administration at the same rate as stovarsol (acetarsone). It is less toxic but has much more powerful amoebicidal properties, its therapeutic index being eight times as favourable as stovarsol. In amoebic dysentery the drug is administered by the mouth in a hard gelatine capsule in doses of 0.25 gm. twice daily for ten days so that a total of 5 gm. is given. For children and weakly individuals the total dosage is smaller. The average total dose based on body weight is about 75 mgm. per kilogram given in ten days. This dose is a relatively safe one to employ and calculation should be made on this basis of the approximate total amount to be given in one course of treatment. No toxic effects are produced even in person who has some liver injury. The largest dose given without producing any toxic effect was 204 mgm. per kilo. during six weeks. Out of a series of 40 cases treated, all were freed from *E. histolytica* in the stool and remained free for one month after treatment. Concurrent protozoal infection was present in many of these patients. *E. nana* were eradicated in a number of cases, so also were *Chilomastix* and *Iodamoeba butschlii*. *Trichomonas* infection responded favourably to carbarsone therapy in two patients. In cases infested with *Dientamoeba fragilis* and *E. coli* the symptoms subsided. Chopra and his co-workers (1933) tried carbarsone in a number of cases of chronic amoebic dysentery with vegetative and cystic amoeba in the stool; 0.25 gm. of the drug was given twice daily for

10 days, the criterion of cure being six negative examinations during a fortnight following the treatment. In a series of 31 cases a ten-day course cured 74.2 per cent. of cases, 12.9 per cent. remained indeterminate and a similar percentage uncured. The proportion of probable cures to failures in this series was 5.75 : 1, as compared with 3.5 : 1 obtained by Knowles in a similar series with emetine bismuth iodide, and 3.16 : 1 obtained by Acton and Chopra with kurchi-bismuth-iodide.

Toxic effects. On laboratory animals no untoward symptoms have been noted following its continued administration within therapeutic range. With doses approaching the M.L.D. by the mouth (150 mgm. per kilo. in guineapigs, 200 mgm. per kilo. in rabbits and from 200 to 250 mgm. per kilo. in cats), the animal may present symptoms of lethargy, loss of weight, abdominal distension, diarrhoea, sluggish reflexes, and failure of the pupil to response to light. Histological examination of animals dying from such doses revealed some renal necrosis and tubular degeneration. On repeated oral administration of doses within therapeutic range (50 mgm. per kilo. daily for ten days in monkeys) no toxic symptoms were observed and in rabbits after 30 mgm. per kilo. daily for ten days no evidence of tissue injury was found.

Cautions and contraindications. Since it contains a substituted amino group in para position to the arsenic atom, it must be used with caution till it is established that it does not act on the optic nerve. As with arsenicals generally, it is contra-indicated in the presence of kidney or liver disease; it should not be used in amoebic hepatitis.

Compounds of mercury. The antiseptic action of mercury compounds is well-known and many of them have been tested *in vitro* in the hope of getting a compound which is more parasitotropic and less organotropic, but none of them have been found effective in amoebic dysentery.

Mercurochrome 220 has been tried in the treatment of amoebiasis. For detailed description see the section on mercury.

Kaolin, also known as 'bolus alba', is a native hydrated aluminium silicate purified from sandy matter by elutriation. Extensive deposits are found in China. It occurs as smooth white or yellowish white powder or in lumps, insoluble in water, in cold dilute acids, and alkaline hydroxides. It is a powerful adsorbant and has an earthy clay-like taste and odour when moistened. Internally it is used in doses of 3/4 to 1 ounce (8 to 30 gm.) with water, milk or gum acacia emulsion. It is best given on an empty stomach. Kaolin and talc (a purified native hydrous magnesium silicate) have been given as a substitute for bismuth in gastro-intestinal affections; both are insoluble and unaffected by acids. Kaolin along with charcoal, talc, kieselguhr, etc., has a remarkable power of adsorbing toxins and antitoxins. Diphtheria toxins and antitoxins are adsorbed by animal charcoal but not by kaolin, talc, kiesel-

guhr or wood charcoal. Tetanus toxin is adsorbed by all the above agents. In general gram-positive bacteria are adsorbed much more readily than the gram-negative. Colloidal kaolin has been tried intravenously in septicæmic conditions, but it has a direct hæmolytic action on the blood; it also tends to produce allergic shock.

On account of its adsorbing power kaolin has been given by the mouth in the treatment of acute bacillary and amoebic dysentery in doses of 20 to 30 gm. stirred in water after a preliminary cleansing of the bowels with calomel. It is particularly useful in cases where a large number of stools have been passed and symptoms of toxæmia are present. It is undoubtedly useful in chronic cases. Asiatic cholera has been treated by kaolin, 400 to 800 gm. being dissolved in a litre of water; three ounces or a wineglassful of this suspension is given every half hour till symptoms abate, then every hour or every two hours up to 12 to 15 hours. In a series of 41 cases similarly treated with kaolin 1 death occurred, while of 24 treated with hypertonic saline 7 died. It is said to have the property of absorbing bacterial toxins and improving the general condition of the patient. Rectal injections of the same suspension have also been recommended in this disease. The action appears to be entirely mechanical. It is also useful in diphtheria, ptomaine poisoning, bacillary diarrhoea, etc.

Osmo-kaolin or colloidal kaolin also has been tried. A commercial variety of this is called *collasan*. The dose should be a teaspoonful or more in water, two or three times a day, combined with an aperient if necessary. Colloidal kaolin should contain no organic or inorganic matter and should give no growth of bacteria either aerobically or anaerobically. This preparation is a very efficient absorbent of bacteria and toxins and has been used with advantage in chronic intestinal disorders and for healing ulcerations of the mucous membranes. A useful prescription is, osmo-kaolin 3½ ounce, tragacanth mucilage 1 ounce, peppermint oil 10 minims, water 8½ ounces. A wineglassful of this is given every 6 hours. Osmo-kaolin has also been tried in amoebic and bacillary dysentery as well as in rheumatism and gout. It can be substituted for bismuth carbonate in the combined treatment with emetine and bismuth.

Kaylene is described as activated colloidal aluminium silicate. It absorbs toxins and is said to act as an intestinal antiseptic. It has been recommended in chronic dysentery, diarrhoea and also for Asiatic cholera.

Sil-Al. Dose 1 drachm (4.0 gm.) in water, half an hour before meals, is used for the same purpose as kaolin.

Rivanol (2-ethoxy-6: 9-diamino acridine lactate) was originally prepared as an antiseptic. A 1 in 1,000 solution kills *E. histolytica* in cultures in 20 to 24 hours. Experiments on cats infected with *E. histolytica* did not prove definitely its curative effect when given per rectum. It produced spasmodic contractions of the smooth muscle of the gut very similar to those produced by papaverine.

Peter (1928) gives a lengthy account and discussion of its use in the treatment of a small series of cases of dysentery in adults, children and infants, clinically and microscopically amoebic in origin. A 1 in 10,000 solution used as rectal enemata, 3 to 6 times daily for 3 to 4 days, cause the disappearance of amoebae and cysts; spasmodic contractions of the colon however occurred. In order to receive rivanol treatment, ambulatory patients must be put to bed for at least half the day. Tenesmus is controlled by tincture of opium. A preliminary cleansing non-irritating enema is given. In adults 1 in 2,000 solution of rivanol in distilled water is the best; 500 to 800 c.cm. of this solution at body temperature are given per rectum, the patient lying on his back or side. If ulceration of the caecum or ascending colon is present, the knee-elbow position is the best. The injection must be retained as long as possible, at least 15 minutes. In every case there was rapid amelioration of clinical symptoms, the temperature came to normal, pain and tenesmus disappeared and stools became normal. In two to three days following this treatment, vegetative and encysted forms of amoebae are said to have disappeared from the stools. It is claimed to be directly amoebicidal, having in addition a sedative and anaesthetic action on the inflamed and irritated gut.

Rivanol has also been given by the mouth both in amoebic dysentery and non-specific mucous colitis. After a saline purgative, 0.05 gm. of rivanol is given 3 times a day for 4 to 8 days, up to a total of 0.9 to 1.7 gm. Cure of amoebic dysentery is said to have been obtained but the results have not been confirmed.

Di-Hydranol. (2-4 dihydroxyl-phenyl-n-hepatone), is given in doses of 0.3 gm. in capsules 2 or 3 times a day for seven days in amoebic dysentery, a total of 14 to 10 gm. being required. It is believed to have a specific effect on *E. histolytica*.

Heptyl resorcinol. Faust (1930) offered evidence that heptyl resorcinol is very successful clinically in amoebiasis. Of the many compounds only hexyl, heptyl and octyl resorcinol are available. The toxicity of these compounds on oral administration appears to increase with the increase in size of the alkyl radicle. Octyl resorcinol may be definitely ruled out because of its local irritating effects. In natural *Balantidium coli* infestations in guinea-pigs heptyl resorcinol was found to be definitely curative, but in doses approaching the M. L. D. hexyl resorcinol is less toxic than heptyl, has a stronger antiseptic action and is worthy of trial.

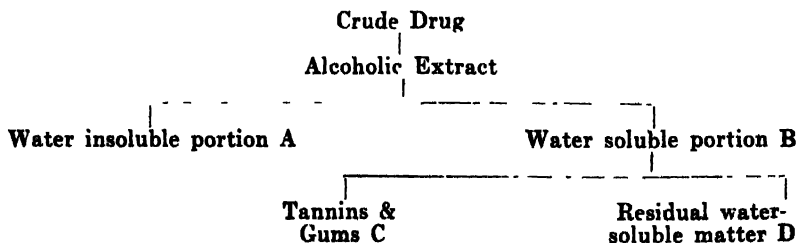
CHAPTER VIII

PALLIATIVE REMEDIES IN AMŒBIASIS

As a considerable residuum of cases of amoebic dysentery is left uncured, Heury and Brown (1924) examined a number of reputed remedies against this disease.

Monsonia ovata and *Rhyncosia adenodes* are used in South Africa, *Brucea abyssinica* and *Brucea sumatrana* are used in Abyssinia and Malaya respectively. These four drugs have been examined chemically without showing any active constituent to which their amoebicidal action could be attributed. *M. ovata* is another of these remedies and a substance called *entericin* was isolated from it, but *entericin* is an ill-defined substance. From the two species of *Brucea* mentioned above, amorphous hitters have been isolated, but trials on free-living protozoa show them to be quite inactive either alone or in the presence of alkali.

The bark of *R. adenodes* was examined by Henry and Brown, but no active substance other than tannins was found. These investigators tried to combine biological and chemical methods with the hope of selecting from the large number of such available drugs any which seemed promising enough for detailed examination. The finely ground drug was exhausted with boiling alcohol and the extract concentrated *in vacuo*; the thick syrup thus obtained was diluted with water to precipitate resinous and fatty matter and this gave preparation A. The liquor was further concentrated *in vacuo* to remove all alcohol, and this was B. This was treated with lead acetate to remove all tannins and this preparation was C and the residue after recovering the precipitate and removing excess of lead was D.



The strength of this final product was adjusted so that 1 c.cm. represented a certain quantity of the drug. All four portions were then tested on glaucoma, an actively motile ciliate occurring in hay infusions. A and D proved non-toxic to this organism and B and C were toxic. The activity was found to be due to one of the components of C and on testing it was found to be the tannin fraction.

It is interesting to note that the action of many of the drugs used against non-specified dysenteries in India and elsewhere is due to their astringent effects and not to the toxic effects of any of their constituents, on the parasites. The chemistry of tannins is still not very advanced. Only a few tannins are obtained in pure condition, e.g., gallotannin (from galls) which can be obtained commercially in crystalline form; ellagic acid, chebulinic acid (from myrobalans), catechin (from Gambier catechu) can also be obtained in more or less pure form. Some of the tannins are readily soluble in cold water and these are in most cases toxic to glaucoma; other soluble in boiling water are non-toxic. The crystalline and sparingly soluble tannins have little or no action on glaucoma. The toxicity to tannins appears to be the inherent property of these compounds, but their action is not very powerful. They kill glaucoma in dilutions of 1 in 1,000 to 1 in 2,000, while the alkaloid conessine from *H. antidyenterica* kills in 1 in 120,000 or more. In view of these facts it appears to be unlikely that any of these tannins or the vegetable drugs which contain them will prove to be of any great utility in resistant forms of amoebiasis.

PLANTAGO OVATA

This is known in the vernacular as *Ispaghula* or *Isabgul*. It is a Persian herb which also grows in the Punjab, Sind and the United Provinces. The seeds which are commonly used are imported from Persia into Bombay in large quantities. In the Tibbi books the seeds are found described under the name of *Bac-i-kaluna*. They are boat-shaped and generally pinkish grey, but the colour may vary, some being brown while others are nearly white with a pinkish tinge, the latter are preferred. *Isabgul* is a well-known and popular remedy in chronic dysentery in India. So commonly is it used in this condition even by Western practitioners that it has found its way into the British Pharmacopœia. When steeped in water the seeds swell up giving out large quantities of a sticky, bland mucilaginous substance with no taste or odour. The seeds of several other species of the same genus exhibit similar properties; *Plantago amplexicaulis* grows in many parts of India and furnishes the brown variety of seed; *P. major* (Luhuriya) grows in the Himalayas; other species of plantago are *P. psyllium* (which is practically the same as *P. major*), *P. brachyphylla* and *P. lanceolata*.

The pericarp which contains all the mucilaginous matter is removed from the seed and is sometimes prescribed instead of the whole seeds by indigenous practitioners. When the seeds are roasted they are said to have a more astringent effect.

Chemical composition. The seeds were examined by Henry and Brown (1923). The chief constituent is the mucilage which is con-

tained in the cells of the epidermis. After excluding the mucilage they could find no active principles toxic to protozoa except tannins. The author found a glucoside named *aucubin* in small quantities.

Pharmacological action. The jelly-like substance occurring in the seeds is acted on by the digestive enzymes to a very slight extent and therefore most of it passes through the small intestine unchanged. It is also not acted on by the intestinal bacteria such as *B. coli*, *B. shiga*, *B. flexner*. The seeds coat the surface of the ulcer and also adsorb the toxins present in the gut.

Therapeutic uses. The seeds on account of their emollient and demulcent effects, are commonly used in India as a remedy in chronic diarrhoea and dysentery. They are thoroughly cleaned from sand and grit with which they are always mixed. Two to 4 heaped dessertspoonfuls prepared in one of the following ways may be taken : (1) With a little sugar and shaken up in a cupful of water. (2) The seeds are mixed with water and allowed to stand for 15 to 20 minutes till all the mucilage comes out. The swollen mass is then swallowed. (3) A mucilaginous decoction made by boiling one to two tablespoonfuls of the seeds in 2 pints of water till the volume is reduced to half. This is given in divided doses, and is preferred especially in acute dysentery.

The first method is preferable as it allows the seeds to mix with the intestinal contents thoroughly so that they spread over the whole of the surface of the mucous membrane evenly; whereas if the mucilage is allowed to form before administration it forms a sticky mass which is not evenly distributed and much of the demulcent action is lost. The drug has no amoebicidal effects and its action appears to be entirely mechanical. The irritated or ulcerated surfaces of the intestinal mucosa are soothed by the demulcent action of the mucilage, which is not acted on by the intestinal juices. It covers the surface of these ulcers and in this way protects them from further irritation. The drug is tasteless and is equally suitable for children and adults.

There is little literature on the use of this drug in dysentery, but it has been unanimously acclaimed as having a remarkably beneficial action in chronic dysentery. The author has given extensive trials to the seeds in chronic diarrhoea and dysentery with excellent results and strongly recommends this drug in chronic irritative diarrhoea and dysentery of both amoebic and bacillary origin. In chronic spastic constipation the drug produces a laxative action. It should be remembered, however, that unless sufficiently large quantities of the seeds are taken no action is produced. One or two heaped tablespoonfuls may be given at a time once or twice daily. It has a laxative action similar to agar.

A number of proprietary preparations composed of the mucilage containing principle of the seeds have been recently put on the market.

AEGLE MARMELOS

It is commonly known as 'bæl' tree and has many vernacular names, *Billwaphal* or *Sripthal* in Sanskrit, *Bæl* in Hindi and Bengali.

The tree is indigenous and is cultivated all over India. In Hindu medicine the root bark is used in the form of a decoction as a remedy in hypochondriasis, melancholia, intermittent fever and palpitation of the heart. The leaves are made into a poultice and applied to the inflamed parts. The medicinal properties of the fruit have long been known to Hindu physicians. Two kinds of the fruit are found in the bazar—a small and wild variety, and a large cultivated variety. The full grown fruit of either variety, when it just begins to ripen, is best for medicinal purposes. It is used in two forms.—

(1) *The unripe or half-ripe fruit.* This is regarded as an astringent, digestive, and stomachic and is an excellent remedy in irritation of the alimentary canal owing to the presence of tannins or mucilaginous substances. It is sometimes used in combination with opium by Ayurvedic practitioners.

(2) *The ripe fruit.* This is sweet and is considered as aromatic and laxative. The dried pulp is pale yellow or flesh-coloured and when mixed with water yields a pleasant orange coloured 'sherbet' which has slightly laxative properties.

Both unripe and ripe fruits contain tannin in small quantities. The dry pulp moistened with cold water yields a red liquid chiefly containing mucilage and probably 'pectin', which separates if the liquid is concentrated by evaporation. As far as is known the principal constituent of bæl fruit is mucilage. Henry and Brown (1923) found only small quantities of tannins present in the ripe fruit, some of which were toxic to glaucoma. More recently Dutt & Dikshit (1930) found in the pulp, besides the usual constituents, a body known as *marmelosin*.

Therapeutic uses. The fruit is said to have an astringent action and this property is not lost by drying, although fresh fruit is preferable. It is said to possess a remarkable efficacy against chronic dysentery and diarrhoea; so commonly was it used by Western practitioners in India in old days that it was included in the British Pharmacopoeia in the middle of last century. It was believed to be an invaluable remedy in obstinate cases of chronic diarrhoea and dysentery unattended with fever, and was given in the form of a powder or as a confection. There is very little literature available regarding the effects of 'bæl' in amoebic dysentery. During recent years the drug has not been tried on a large scale and controlled by proper examination of stools. It has little or no effect in acute dysentery, though the powder is said by some to produce good effects in this condition. The first noticeable effect is that blood rapidly disap-

pears and the stools assume a more fæculent form. Fresh fruit is considered by some to be more efficacious than dried fruit. The main action of the drug in chronic dysentery is due to its demulcent properties and also to a certain extent to the tannins present in it. The drug is worthy of trial in chronic amœbiasis where other remedies have failed.

Preparations.

(1) **Extract of bæf.** This is made from fresh unripe fruit. Dose $\frac{1}{2}$ to 1 drachm 2 to 3 times a day.

(2) **Liquid extract of bæf.** This is prepared from dried slices of unripe fruit. Dose $\frac{1}{2}$ to 1 drachm several times a day. It is said to be much less effective than the fresh extract.

(3) **The powdered dried pulp.** This is said to keep well in air-tight bottles. Dose $\frac{1}{2}$ to 2 drachms in chronic dysentery.

Decoction of the dried bæf fruit and syrup made with fresh or dried fruit are also used.

ACORUS CALAMUS

It is commonly known as 'sweet flag', in English, 'Bach' in Hindi and Bengali. It is a semi-aquatic perennial herb with an indefinitely branched rhizome. It is really a native of Europe and North America, but is cultivated in damp marshy places in India at an altitude of 3,000 to 6,000 feet; it has established itself on the edges of lakes and streams. The long creeping horizontal rhizome is collected in the autumn, cut into pieces and dried.

Chemical composition. The dried rhizome yields 1.5 to 3.5 per cent. of a neutral yellow aromatic essential oil having an agreeable odour. The chief constituent of this oil is asaryl aldehyde. There is also a bitter glucoside named acorin and certain other substances, such as eugenol, asarone, pinene and camphene are present. The drug contains abundance of starch and a little tannin. Henry and Brown (1923) found an essential oil which was toxic to glaucoma but no other active principle except tannins.

Therapeutic uses. The rhizome is emetic, nauseant, anti-spasmodic and carminative. In doses of 35 to 40 grains it produces a violent and persistent emesis; it has an expectorant action and is used as a remedy for asthma. The drug is a very old remedy for chronic diarrhoea and forms part of a number of mixtures in the Hindu medicine. Evers (1875) tried it in chronic dysentery with good results. It has been discarded in recent years, and any effect it produces is due to the presence of tannins.

HELICTERES ISORA

It is commonly known as the East Indian screw tree belonging to the Sterculiaceæ family. In Hindi it is known as *Marar* or *Mararphall* (or the pod used in dysentery), in Guzrati it is known as *Mriga shingha* or deer's horn. It is a tall shrub, or a small tree resembling the common hazel. It has bright red and showy flowers which appear in the rainy season. The plant grows in Western India and in Kashmir. According to Ainslie it is used by Hindu physicians as a remedy for offensive sores inside the ear. It also forms part of prescriptions used for the cure of griping in the bowels and flatulence especially in children. The pods have demulcent and slightly astringent properties.

Chemical composition. The author analysed the pods, but no active principles with the exception of tannins and the demulcent substances could be discovered.

Therapeutic uses. The pods are used in some parts of India in the treatment of chronic dysentery. In some patients the symptoms are considerably ameliorated.

CASTELA NICHOLSONI

This plant is known as *Chaparo amargosa* in Mexico and was used by Mexicans in the treatment of dysentery. It is a semi-rubiaceous plant and its active principle is a glucoside called *castelin* and a bitter principle called *castelamarin*. Castelin crystallizes in long white needles and dissolves in 85 parts of water and is also soluble in alcohol. It is dextro-rotatory and is readily hydrolysed by dilute acids, yielding *castelagenin*.

Pharmacological action. Schneider (1925) found castelin, and castelagenin to be toxic, death being produced in animals from gradual paralysis, the respirations ceasing before the heart. Under the microscope 1 in 10,000 of the detannated fluid extract caused loss of movements of *E. histolytica* and the assumption of a spherical form. These observations have not been confirmed by other workers.

The 'chaparo' (any part of the plant, root, leaves, bark), is powdered and measured in heaped teaspoonfuls. Five teaspoonfuls are given daily, i.e., three as drinks, each prepared by boiling a teaspoonful of the powder in 8 oz. (240 c.c.) of water for a quarter of an hour and two for enemata similarly prepared with 12 oz. (360 c.c.) of water. The decoction is cooled and strained before administration. The enema is given by a long rubber catheter, passed as high as possible, with the patient in the knee-elbow position. The drinks are given half an hour before breakfast, lunch, dinner and supper and enemata at 10 a.m. and 6 p.m. The treatment is continued for 10 consecutive days. The decoction has a very bitter taste. Some cases, apparently incurable with emetiae, appear to have been benefited by 'chaparo'.

SIMARUBA BARK

Simaruba bark is obtained from various species of Simaruba, *S. officinalis*, *S. amara*, *S. glauca*, etc. It was brought to Paris in 1713 from Guiana, where it was said to have been used with success by the natives in the treatment of dysentery. It soon gained a reputation in Europe and was imported in large quantities. The active principle of the bark is a crystalline bitter substance possessing neither alkaloidal nor glucosidal properties. It has been used in amoebic dysentery with some success in a similar manner as 'chaparo', a handful of bark being cut up and a decoction prepared in the same way. It does not produce any marked therapeutic effects in this disease and is now seldom employed.

Uzara is another African plant belonging to the N. O. Asclepiadaceae. It is a proprietary article recommended by certain German workers, but is of doubtful efficacy.

CHAPTER IX

DRUGS USED AGAINST FLAGELLATE DIARRHŒA

These may also be considered here. There has been a considerable amount of difference of opinion regarding the pathogenicity of intestinal flagellates present in the human gut. Although they are undoubtedly present in large numbers in irregular diarrhœa especially in children, it is doubtful if they are the causal organisms. The two flagellates most frequently met with are *Giardia intestinalis* and *Trichomonas hominis*, the former being believed to be pathogenic. The organisms are not always limited to the intestinal canal and *Lambli* (*giardia*) *intestinalis* has been found in the gall bladder and bile ducts, liver abscesses, pleural exudates, etc. In children they produce intermittent diarrhœa infection being carried through cysts and the house fly. As proof of their pathogenicity it has been pointed out that in *Lambli* infections the stools are often pale and pultaceous, having a characteristic odour; most of the cases show eosinophilia, which disappears after treatment. Inoculation in cats per rectum or feeding them with *Giardia intestinalis* and murtis produces severe diarrhœa which may be fatal. Autopsy shows inflammatory and necrotic changes in the bowels containing active stages of the flagellates throughout.

Chilomastix mesnili, another human flagellate, may cause diarrhœa although it has been considered harmless. Various trichomonas have been found in the intestines, biliary passages, mouth, vagina and bladder.

Treatment. The course of these diarrhœas is irregular and it is very difficult to say whether a drug has caused disappearance of the flagellates or not. Many drugs have been tried in these cases. Essence of turpentine is beneficial, but the results may be temporary. Carbonate of bismuth in doses of 30 to 90 grains daily for one or two months has been suggested. The drug is stopped every 10 days, and bile and calomel are given in the interval to stir up the lurking parasites. Bismuth salicylate in doses of 10 grains 3 times a day has been recommended, several courses of one week or 10 days being given during a period of six months. Arsenical preparations such as arsphenamin and neoarsphenamin, in the usual doses intravenously, can be tried; it is better to give a desensitising dose of 0.2 gm. first. Stovarsol is given in doses of 0.5 to 0.75 gm. daily on the first three days and 1.0 gm. daily for next three or four days, the course being repeated with four-day intervals between each up to three weeks. Treparsol in the usual doses has been reported to be a specific in giardia and trichomonas diarrhœa. Carharsons in 0.25 gram doses 2 or 3 times a day

for 10 days has been recommended. Thymol in form of enemata (1 in 2,000 solution) and orally in doses of 0.25 to 0.5 gm. has been tried. Yatren and carbon tetrachloride in 20 minim doses in children and 5 c.cm. doses in adults, followed by magnesium sulphate, gave temporary beneficial effects. Disappearance of both trichomonas and Giardia on pure meat diet has been observed when the condition is associated with faulty carbohydrate digestion.

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SECTION II

REMEDIES USED AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS

REMEDIES USED IN LEISHMANIASIS

Since the discovery of the causal organism of kala-azar by Leishman and Donovan in 1903 our knowledge of this species and the genus leishmania has rapidly increased. At the present time at least three distinct species are known to occur in man, viz., *L. donovani*, *L. tropica* and *L. braziliensis*. *L. donovani* is the cause of kala-azar or visceral leishmaniasis as found in parts of India, China and the Mediterranean littoral. There are also a few small areas where the disease has been found in Turkestan, the Sudan, etc. *L. tropica* (Wright) causes the cutaneous infection known as 'Oriental sore,' Delhi-, Lahore-, Frontier- or Bagdad sore, Aleppo boil. *L. braziliensis* is the cause of American cutaneous leishmaniasis, which causes secondary ulceration of the muco-cutaneous areas of the nose and mouth.

Still another manifestation of cutaneous leishmaniasis due to the species *L. donovani* is found in India as a sequel to kala-azar. This condition occurs in anything up to 5 per cent. of cases of kala-azar. A certain number of patients presenting themselves for treatment of this condition deny any previous history of kala-azar; many give a history of fever of a long-continued nature, with enlargement of the spleen. As a certain number of cases of kala-azar are known to recover without treatment, the probable assumption is that these cases are the sequel of a transitory attack of kala-azar when the patients' natural resistance has brought about a cure of the generalised disease.

As found in man and other vertebrate hosts, the parasite is a minute oval protozoon about 3μ by 2μ . They are found in the endothelial cells of the vascular and lymphoid tissues, in

the liver, spleen and bone marrow. In culture and in arthropod hosts the organism develops into a flagellated form.

Recent work in India has incriminated the sandfly *Phlebotomus argentipes* as a vector of *L. donovani*. Much evidence has also been accumulated which incriminates the sandfly *P. papatasi* as the vector of *L. tropica*, and it is very probable that other species of the genus *Phlebotomus* will be found to be vectors of leishmaniasis in other parts of the world.

That a certain amount of immunological resistance is developed after an attack is well known. The number of instances in which a second attack of kala-azar has occurred is negligible and it is a well-known fact that once a person suffers with oriental sore he is most probably protected for life.

Visceral leishmaniasis or kala-azar is a terrible scourge in India and has been responsible for a very high mortality. Without treatment the prognosis is usually death within two years. The use of antimony, especially the pentavalent compounds, in kala-azar constitutes one of the most important advances in chemotherapy and has revolutionised the treatment of the disease. To produce its curative effect antimony must penetrate the endothelial cells in which these organisms are living.

CHAPTER X

ANTIMONY AND ITS DERIVATIVES

Antimony has a very interesting history. Grey antimony has been used from the earliest times in the East as an 'eye salve' for protection against endemic eye diseases and as a remedy for oriental sore. In the 16th and the 17th centuries antimony was considered as a panacea for many diseases, *c.g.*, syphilis, leprosy, plague, cancer, ague, perhaps a forecast of its most recent use in chemotherapy. As early as 1631 the preparation, antimony tartrate or *lartar emetic* came into existence and by the end of the 17th century more than a hundred preparations of antimony were in use in medicine, chiefly against plague and other infectious fevers. Owing, however, to its indiscriminate use many deaths occurred and it was discarded to a great extent, and in many places its use was actually prohibited. During the last two decades antimony compounds have proved very useful in the treatment of some of the tropical diseases of parasitic origin, such as trypanosomiasis, leishmaniasis, bilharziasis, etc. The compounds largely used till lately were the double tartrates of potassium and sodium, for the obvious reason that being double salts they are not readily dissociated, and therefore have not such marked irritant or corrosive properties as the inorganic salts. They, however, suffer from certain disadvantages, one of the chief being that small doses, a maximum of $2\frac{1}{2}$ grains, can only be given at a time, and the treatment is very protracted in such diseases as trypanosomiasis, where a high concentration of antimony in the body, maintained for a long time is necessary to produce the desired therapeutic effects. Subcutaneous and intramuscular injections of these compounds are extremely painful, and even when administered in oil, are very unsatisfactory. Intravenous administration, which is a more difficult procedure, is the only method by which they can be given. It is for this reason that efforts have been directed

towards preparing such compounds as can be administered readily in fairly large doses, without producing untoward effects, so that the therapeutic effects are rapidly attained.

Pharmacological Action

The action of the antimony ion in the main resembles that of the arsenic ion, the chief differences lying in its stronger local irritant effects and more difficult absorption.

Action on protozoa. The salts of antimony, arsenic and bismuth have been shown to have special affinity for certain pathogenic protozoa. Antimony destroys trypanosomes in drawn blood in such high dilutions as 1 in 500,000. The non-pathogenic protozoa such as the paramoecium are not affected even by concentrations of 1 in 5,000. It would appear therefore that these compounds have a true specific effect against pathogenic protozoa in the same way as quinine has against the malarial parasites. Antimony compounds are effective against a variety of protozoal infections met with in the tropics.

Externally. When rubbed into the skin, antimony salts produce a characteristic inflammation, at first papular then vesicular and lastly pustular, the rash looks like the eruptions of smallpox. Given subcutaneously, the salts give rise to severe pain and inflammation, often followed by suppuration and sloughing. Salts such as the chloride act as powerful escharotics.

Internally. When given by the mouth tartar emetic has an acrid metallic taste and in very small quantities it produces no symptoms except perspiration. The stomach experiences a slight sensation of soreness, a sensation easily mistaken for hunger. In somewhat larger doses it produces increased secretion of mucus from the stomach and the intestines. Diarrhoea with colic is produced, numerous liquid motions being passed. The secretion of the bronchial mucous membrane is increased and the secretion of most mucous membranes is enhanced. Large doses (2 to 3 grains) give rise to nausea and vomiting accompanied by marked depression and the usual accompaniments of emesis, *e.g.*, salivation, profuse perspiration, acceleration of the pulse, etc. All these symptoms are produced reflexly through the medulla. As an emetic the action of tartaremetic is somewhat tardy taking 8 to 20 minutes and sometimes half an hour; hence in cases of poisoning it is unsuitable as an emetic and is never used. The emesis is produced by the direct irritant action of the drug on the stomach.

Absorption and distribution. In the stomach, antimony is slowly dissociated and produces irritation, hyperaemia and swelling of the mucosa. The acid reaction of the gastric juice probably facilitates this process; dissociation also occurs in the intestines

where the reaction is neutral or alkaline. As a rule vomiting removes the compound from the stomach and very little passes into the intestines, but when it does it produces diarrhoea and colic. Absorption of antimony is very slow from the skin or from the gastro-intestinal tract. As it is too irritating to be administered by subcutaneous or intramuscular routes, the intravenous route is the only possible one. Fortunately the toxicity of these compounds when given by this route is very low, as large amounts are rapidly excreted by the kidneys. From the blood, antimony passes into the tissues much more slowly than arsenic. It is found in considerable quantities in the liver and the spleen especially if administered in metallic form. The volume of both the liver and the spleen is considerably increased after intravenous injections and the automatic movements of the latter organ are stimulated.

Circulation. The cardio-vascular effects produced by antimony resemble those produced by arsenic, but acceleration of the pulse seen after tartar emetic is a reflex effect due to the emetic action and not to the absorption of the antimony ions. When injected into a vein, antimony acts directly on the cardiac muscle and capillaries, producing a slow and weak pulse; the heart muscle is depressed, the capillaries are dilated. There is paralysis of the walls of the arterioles due to its direct action on the muscular coat; the vessels of the splanchnic area are particularly affected. The blood pressure falls on account of vaso-motor paralysis; tachycardia may occur and may be distressing. The heart becomes weak and rapid at first, and is later slowed, the contractility of the cardiac muscle is eventually destroyed and the heart stops in diastole.

It is possible that dissociation of antimony compounds occurs in the blood and the antimony ions combine with the proteins of the plasma. The alkalinity of the blood and the number of erythrocytes are said to decrease while the leucocytes are said to be increased.

Tartar emetic and organic antimony compounds do not hemolyse or agglutinate erythrocytes either *in vitro* or *in vivo*. Concentrations as high as 1 in 20 have no effect on either washed or unwashed corpuscles, and intravenous injections of 0.02 gm. per kilo. produce no intravascular agglutination.

Respiration. There is slight initial acceleration but soon there is nausea and the respiration becomes shallow and irregular. In cases of poisoning, respiration is very slow, laboured and finally ceases along with the stoppage of the heart. Intravenous injections stimulate the respiration slightly; large doses produce marked congestion and oedema of the lungs, in fatal cases of poisoning.

Secretions. The secretions such as perspiration, saliva, mucus, sputum, bile, etc., are increased. The increase of saliva and perspiration are generally reflex being secondary to nausea, although a part of

the increased activity of salivary and other glands may be due to the direct stimulating action of the antimony ions eliminated in them. The quantity of urine is increased with small doses; with large doses it is decreased and may even be suppressed.

Metabolism and temperature. The effects of antimony on metabolism have not been studied so thoroughly as those of arsenic, but antimony compounds seem to present a strong resemblance to the arsenicals. The non-protein nitrogen of the blood is said to be increased in some cases after intravenous injections, and very small quantities given repeatedly by the mouth are said to increase the glycogen and fat content of the liver without apparently altering the rate of excretion of nitrogen in the urine. Prolonged use of toxic doses produces fatty degeneration of many organs, probably owing to diminished oxygenation and metabolism.

Antimony salts have a distinct antipyretic effect. Vomiting is also accompanied by a fall of temperature which may amount to 1°C. (1.5° to 2°F.). During the collapse stage the temperature may fall much below normal because of the slowing of the heart, dilatation of peripheral capillaries and increased perspiration.

Central nervous system. In the frog, subcutaneous injections of the double tartrates produce initial stimulation of the medulla followed by paralysis; later, the spinal cord and the motor ganglia of the brain become paralysed and the reflexes are lost. In mammals, its effects are more obscure. The animals generally die of convulsions, from respiratory and cardiac failure, but it is difficult to say whether these are due to the action of the drug on the central nervous system or due to vascular paralysis or severe gastro-intestinal irritation. It undoubtedly has a depressing effect on the nerve cells even in moderate doses. In cases of poisoning with antimony salts, there is motor and sensory paralysis and loss of reflexes, the latter effect being due to its action on the cord.

Excretion. Antimony salts are mainly excreted by the stomach, the intestines and the kidneys; traces occur in the bile, the sweat and in the milk, and possibly also in the bronchial secretion. There is less danger of cumulative poisoning than with arsenic since antimony is more rapidly excreted. After intravenous injection of 0.12 gm. of tartar emetic, 30 per cent. of antimony is excreted in the urine in 48 hours; of 1.7 gm. injected in a six weeks' course, 1.0 gm. was recovered from the urine. No data are available as regards the quantity excreted by the faeces. It should be used with caution in diseased conditions of the kidneys, the alimentary, the circulatory and the respiratory tracts, especially the former. Large doses produce inflammation of the kidneys accompanied by albuminuria, anuria, and hæmorrhages in the kidney substance.

Action of organic compounds of antimony. Chopra (1927) showed that the action of the organic compounds of antimony, such as urea-stibamine, is in the main the same as that of the antimonyl tartrates. Intravenous injections of most of these compounds produce a fall of blood pressure which is often more marked than in the case of tartrates. The heart becomes slow and irregular, but it gradually recovers and the blood pressure comes to its normal level. All these compounds have a depressant action on the heart, and relax the ventricles in the same way as cinchona alkaloids. There is a marked rise of pulmonary pressure. It is worthy of note that the arsenical compounds such as salvarsan also cause a marked rise of pulmonary pressure, and this is of interest in connection with 'nitritoid crisis.' Acute toxic symptoms resembling 'nitritoid crisis' are rare with the tartrates, but they are not uncommon when organic compounds are administered. It is quite likely that these symptoms are due to changes occurring in the pulmonary circulation. After an intravenous injection of organic antimony compounds, the respiration stops momentarily and then restarts, being somewhat depressed at first but regaining its normal amplitude.

On the spleen and the liver the effect of these compounds is noteworthy. In experimental animals there is a well-marked increase in the volume of the spleen accompanied by increase of rhythmic movements; the same is the case with the liver though the effect is not so apparent. The effects produced are more marked in case of the organic compounds than with the antimonyl tartrates. After injections of antimony compounds in human subjects, the patients often complain of a feeling of pain and a sensation of distention in the splenic region, and there may also be uneasiness in the hepatic region. These can be accounted for by the increase in the volume and rhythmic movements of these organs. It is possible that this increase has something to do with the therapeutic effects produced by these compounds. The spleen and the liver act as reservoirs of parasites and the influx of blood charged with antimony into these organs may contribute towards the destruction or expulsion of the parasites from these hiding places. It has been found that soon after injections of an antimony compound, Leishman-donovan bodies make their appearance in the peripheral blood where they were previously absent, showing that the action is of a provocative nature.

Antimony has a stimulating effect on the adrenals. It has been shown by Chopra and his collaborators (1928) that the residual epinephrine contents of the supra-renal glands of rabbits, who have had a course of antimony compounds, is higher than those of normal animals.

Tolerance. Continued administration of antimony to mammals does not produce tolerance as is the case with arsenic compounds.

This is due to the fact that the excretion of antimony is not diminished but on the contrary is increased. Rowntree and Abel (1917) have shown that *T. biucci* does not become 'antimony fast.' Kolmer (1926) succeeded in rendering *T. equiperdum* appreciably more resistant to antimony. Tolerance to arsenic does not confer tolerance to antimony. Some of the infusoria become resistant to the action of antimony.

Toxicity. The maximum tolerated dose of tartar emetic for rats, rabbits and guinea-pigs by slow intravenous injection of a 1.0 per cent. solution is about 0.015 gm. per kilo. body weight. For a man of 70 kilos. (145 lbs.) it corresponds to 1.05 gm.; the dose usually given to human beings at one time, i.e., 5 to 10 c.cm. of a 1.0 per cent. solution (0.5 to 0.1 gm.) is therefore well within the range of safety; such a dose would be 10 to 20 times smaller than the maximum tolerated dose and it may be safely repeated. Cases of poisoning are due to increased susceptibility of individuals and deaths have occurred from 2 grain doses given intravenously. It is, therefore, advisable to start with such small doses as 1 to 2 c.cm. of a 1.0 per cent. tartrate solution, and corresponding doses of other compounds. Repeated doses in animals produce changes in the kidneys and in the liver similar to those produced by the arsenical compounds. Epithelial degeneration has been observed, sometimes going on to fatty degeneration. Jaundice has not infrequently been noticed in kala-azar patients after a course of injections with antimony compounds and sometimes ascites has followed. The lungs may show hyperæmia and œdema. Brahmachari (1922) found marked pathological changes in guinea-pigs after toxic doses of antimonyl tartrates, consisting chiefly of hæmorrhages in the substance of the internal organs and destruction of the parenchyma of the lungs, kidneys, liver, pituitary and suprarenal glands. Similar changes are produced by the new pentavalent aromatic organic compounds.

Poisoning in man. The symptoms of acute poisoning resemble those of arsenic; these generally begin with nausea, vomiting and pain in the stomach, which is not relieved by vomiting. Emesis is violent and continuous, the ordinary contents of the stomach are first evacuated, then slimy mucous fluid which later may contain blood. In some cases no gastric symptoms are observed, but these are very rare. Vomiting is accompanied by profuse diarrhœa, followed by great muscular weakness and collapse. Prostration is intense and the patient repeatedly faints. The pulse and the respiration become slow and irregular, the skin is cold and covered with perspiration; cyanosis of the face and extremities is generally marked, and the temperature is subnormal. The patient falls into a comatose condition which deepens until after a few weak convulsive movements death ensues. The minimum fatal dose of tartar emetic in man by the mouth is difficult to estimate as the greater part of the poison is generally

removed by vomiting. Recovery has been observed after large doses, while in other cases 2 grains have proved fatal.

Chronic poisoning is very rare and difficult to diagnose. It has been observed in type-setters and is usually mistaken for plumbism. The pentasulphide is used in the manufacture of rubber, and antimony salts are also used in glazing cheap granite ware, and in this way may contaminate food stored in them. Since antimony compounds have come into vogue in the treatment of tropical diseases, symptoms of chronic poisoning are sometimes seen. These symptoms are loss of appetite, depression, headache, giddiness, anaemia, confusion, drowsiness and dimness of vision. The patient complains of a feeling of suffocation or a feeling of spasm of the glottis, discomfort or pain in the region of the stomach, general weakness and exhaustion. Profuse diarrhoea may ensue and ulceration of the small intestines round the solitary follicles and Peyer's patches has been found. The blood pressure is low and the blood shows leucopenia and eosinophilia. There may be rapid loss of flesh, dysuria, albuminuria, transient jaundice and paraplegia; pustular eruptions and sometimes collapse after extreme dyspnoea have been observed from prolonged internal use of tartar emetic.

CHAPTER XI

THERAPEUTICS OF ANTIMONY COMPOUNDS

The revival of the use of antimony is a triumph of rational therapeutics, for it was through reasoning from its chemical affinities that Cushney was led to try the remedy in protozoal diseases. Its expectorant action is taken advantage of in acute bronchitis, in which the secretion of bronchial mucus is insufficient, but it is of less value when the secretion is abundant. Its use as a diaphoretic and in respiratory diseases has now been entirely given up. Tartar emetic has been recommended in tuberculosis; keratitis has been treated with injection of tartrates; injections of the tartrates have also been given in cerebro-spinal fever. Antimony compounds have been advised instead of arsenic in the treatment of certain skin diseases. Tartar emetic ointment has been tried locally but it is very irritant and its continued use has led to diffuse subcutaneous abscesses and necrosis. This is due to the fact that the tartrates are split up by the acid secretions, forming more irritant compounds. In leprosy injections of the tartrates are said to produce beneficial effects.

Kala-azar or Visceral Leishmaniasis

Before the introduction of intravenous injections of antimony compounds the disease ran a course unaffected by treatment. Many remedies including large doses of quinine, vaccines, etc., were tried but proved useless. Whatever cures were produced were of a spontaneous nature and these have been estimated as high as 25 per cent. A concurrent attack of pneumonia or cancrum oris sometimes produces a cure. Injections of drugs, which produce leucocytosis, *e.g.*, turpentine, occasionally gave good results.

The treatment of kala-azar is now carried out with two classes of antimony preparations.

Trivalent compounds. Patrick Manson originally suggested the use of antimony salts in kala-azar but Vianna (1913)

was the first to try intravenous injections of tartar emetic, and successfully treated American forms of cutaneous and mucocutaneous leishmaniasis. Di Cristina and Caronia (1915) used this salt and successfully treated visceral forms of leishmaniasis in children, prevalent on the shores of the Mediterranean, by intravenous injections of tartar emetic. In the same year Rogers and Muir took up the treatment of Indian kala-azar with this drug and confirmed the above results. Rogers at first used a 1 per cent. solution, but later he found that a 2 per cent. solution was quite safe and more convenient. Solutions as strong as 5 per cent. can be given intravenously but they are apt to produce cough and retching, and it is not therefore advisable to use solutions stronger than 2 per cent. The solutions may be made in distilled water with or without the addition of 0.85 per cent. of sodium chloride. It is important to use freshly prepared solutions, as moulds are apt to grow and produce toxins. Solutions can however be kept for weeks if 0.25 per cent. of carbolic acid is added at the time of preparation.

Injections were given every second or third day into the veins of the arm or into the jugular vein (in children), the doses being gradually increased from 2 to 5 c.cm. of a 2 per cent. solution, keeping a watch whether nausea and gastric symptoms develop. Later, Knowles (1920) treated many cases in Assam, checking his results by spleen puncture and culture of the material for the presence of *L. donovani*. The effects were marvellous and after a few injections the fever subsided. In some cases rigors followed larger doses, but ceased after a time and the temperature remained at a low level or was normal; the weight of the patient steadily increased and the spleen diminished in size. On puncture of the spleen the number of parasites was found to be reduced; the blood showed a marked increase in leucocytes. The antimonyl tartrates are dangerous if given in doses larger than the patient can bear; the dose should be increased very gradually. Napier recommended for an average adult a primary dose of 2 c.cm. of a 2 per cent. solution (0.04 gm. of the salt), increased on each occasion by 1 c.cm., up to a maximum of 5 c.cm. (0.1 gm.); subsequently 5 c.cm. are given on each

occasion. For debilitated patients the initial dose should be 0.5 c.cm. increased by 0.5 c.cm. up to the maximum of 5 c.cm. For a child of 3 years it is advisable to begin with 0.5 c.cm. making 2 c.cm. the maximum single dose. For children of 12 the maximum is 3.5 c.cm., the doses for intermediate ages being in proportion. The dose calculated according to pounds of body weight is proportionately larger in children than in adults. The injections are given on alternate days throughout the course; they should be given at least twice a week. A routine course of 30 injections is given and a spleen or liver puncture is then done and 2 or 3 N.N.N. tubes inoculated. If no flagellates develop, and the patient's general condition and blood counts are satisfactory, he is considered cured; otherwise a further course of 10 to 15 injections is given and the puncture repeated. As a general rule it may be stated that a maximum dose of 60 grains (4 gm.) per 100 lbs. of body weight is necessary to produce a cure. This maximum course can be modified according to the general improvement in the condition of the patient, the chief factors to be taken into consideration are fever, the size of the liver and the spleen, and the blood picture. If the body weight has increased, the spleen is reduced to the level of the costal arch or at least by 4 inches, the white cell count is above 6,000 and the temperature is normal by the seventh injection, the full course of 4 gm. may be modified to 30 injections (2.88 gm.). If the temperature falls to normal by the tenth injection, 35 injections should be given; and if between the tenth and sixteenth injection, 40 injections are necessary. If this procedure is followed the cure rate is about 80 per cent.

Tolerance is quickly established, and then much larger doses can be given with corresponding beneficial therapeutic effects. In increasing the dosage, the development of tolerance should be judged from the amount of fever, cough and nausea produced. These should not be allowed to be more than slight; in fact, it may be laid down that nausea is an indication for not increasing the dose. The other important considerations are the state of the pulse, lungs and bowels and in serious cases of disease where emaciation is

marked these should be very carefully examined. Heart failure is the most serious of all the symptoms and cardiac stimulants should be freely used if necessary. Intramuscular injections of 0.5 c.cm. to 1 c.cm. of adrenalin are useful in counteracting the vasodilator effect and fall in blood pressure. If hæmorrhagic lesions occur give calcium lactate, 10 grains three times a day or 5 to 10 c.cm. of a 10 per cent. solution of calcium chloride intravenously. If œdema of the feet becomes evident the doses should be regulated with utmost caution. The treatment is continued till the temperature becomes normal. The fever does not as a rule subside before ten injections have been given. In a few cases the temperature may fall after 3 or 4 injections ; in others it may keep above normal till 40 injections have been given. A few cases show a slight rise of temperature after each injection. Among kala-azar patients the complications usually met with are diarrhoea, low blood pressure, bronchopneumonia and sloughing of the connective tissue in the form of cancrum oris. Antimony salts if used injudiciously, accentuate all these conditions, and therefore, great caution is necessary in their administration in such cases. It is of the utmost importance that when treatment is once started it should not be interrupted. Slight diarrhoea, œdema of the feet, bleeding from the gums, traces of albumin in the urine are not contraindications to treatment, in fact, they demand it. In some cases fever and rigors occur after the first injection. This is believed to be due to the destruction of parasites by the compound, as such reactions do not occur in patients who are not suffering from kala-azar, and they become less and less marked as the patients improve.

For the next five years after the introduction of antimonyl tartrates little further progress was made in the treatment of the disease in India. Sodium salts were substituted for the potassium salts and a number of purified brands of the antimonyl tartrates suitable for intravenous injection were put on the market. The greater solubility of sodium antimony tartrate makes it possible to prepare a scale form of the salt. As the purity of the salt is essential for the preparation of the scale form, it gives the practitioner greater security. With scale

preparations the severe reactions met with in the early days of treatment were minimised. A larger number of other antimony tartrates were prepared but they proved to be no more efficacious than the antimony tartrates of sodium and potassium.

Pentavalent or organic aromatic compounds. In the meantime the firm of von Heyden in Germany introduced the first pentavalent aromatic compound of antimony, sodium para-acetyl-amino-phenyl stibiate or 'stibacetin'; this was tried in the treatment of kala-azar, with promising results. Brahmachari (1922) followed up this work under the auspices of the Indian Research Fund Association and prepared a number of pentavalent compounds including urea-stibamine, which later proved to be therapeutically very effective. The introduction of these pentavalent compounds of antimony was an important advance in the treatment of kala-azar and marked the second phase in the treatment of leishmaniasis with antimonials. The advantages claimed for the pentavalent aromatic compounds according to Napier (1927) are:—

- (1) These compounds are much less toxic, and can therefore be administered in larger doses. The minimum lethal dose is 15—25 mgm. per kilo. in mice in the case of the trivalent compounds, whereas it is 200 to 500 mgm. in the case of the pentavalent compounds.

- (2) The total amount of antimony which is necessary to effect a cure can be administered in a much smaller number of doses. About ten doses of the pentavalent compounds against thirty doses of sodium antimony tartrate can be looked upon as the average number necessary for an ordinary case. This reduction in the number of injections means a reduction in the time the patient is under treatment from two months to about three weeks, which in its turn means that a greater percentage of the dispensary class of patients will complete a full course of treatment

- (3) Resistant cases which respond slowly when treated with the tartrates, improve rapidly with larger doses of antimony in the form of the less toxic pentavalent compounds.

(4) Certain disagreeable symptoms, such as coughing and severe joint pains, which are frequently associated with the tartrate treatment, do not occur when the pentavalent compounds are used. In a number of cases these symptoms are so severe that they necessitate the reduction of the dosage to such an extent as to prolong the course of treatment almost indefinitely and reduce considerably the chances of an eventual cure.

(5) The death rate amongst kala-azar patients under treatment has been very markedly reduced since the introduction of the pentavalent compounds. One of the most frequent causes of death during the course of treatment, namely, pneumonia, has been almost entirely eliminated.

Napier (1924) reported a death rate of 14.4 per cent. in a series of 139 cases treated with sodium and potassium antimony tartrate. The same author (1926) found the death rate to be 4.2 per cent. in a series of 167 treated in the Carmichael Hospital for Tropical Diseases, with six different pentavalent compounds.

The disadvantages of pentavalent compounds are comparatively few. The post-treatment jaundice is a little more frequently encountered, but it is not so serious as is the case with organic arsenicals. Anaphylactoid symptoms may suddenly appear towards the end of the course of injections but these are of a mild type. There is only one thing which stands in favour of the antimony tartrates and that is the high cost of the pentavalent compounds. Taking 3 gm. as the total dose necessary to effect a cure, the cost of curing a patient will be a few annas with tartrates against 6—8 rupees in case of the pentavalent compounds. This statement was made in 1927; the present price of the pentavalent compounds is much lower.

Dosage of pentavalent compounds. The initial dose suggested by the makers in the case of urea-stibamine (or stiburea), and amino-stiburea is 0.05 gm., increased by 0.05 gm. at each injection up to 0.2 gm. Napier prefers to start with 0.1 gm. for the first dose, 0.2 for the second and 0.25 for the subsequent injections. With stibosan and neostibosan

an initial dose of 0.2 gm. and subsequent doses of 0.3 gm. can be given. Children should be given smaller doses but they tolerate proportionately larger doses than adults. Infants of 18 months to 3 years of age will tolerate 0.1 gm., children of 6 years 0.15 gm. and children of ten years or over 0.2 gm. In Napier's series, with a total of 2.7 gm. of urea-stibamine and aminostiburea, the relapse rate was very low; with von Heyden 693 and 693B, a total of 3.35 gm. in 10 injections and 2.3 gm. in 8 daily injections gave good results.

Most of the compounds are supplied in sealed ampoules containing the dose required. The top of the ampoule is broken off and the contents are poured into a sterile test tube containing 3 c.cm. of sterile distilled water; not less than 3 c.cm. should be used for 0.2 gm. of the drug. This is sucked up in a sterilised syringe, and injected in the usual way. If ampoules are not available the drug is weighed on a clean piece of paper. The solutions should be prepared at the time of the injection whenever possible, but they can be kept for a few hours.

Urea-stibamine and homologues. There are several brands of this product on the market in India besides urea-stibamine (Brahmachari), 'stiburea', 'urea-stibol', 'stiburamin', have more or less the same composition and action. Brahmachari calls it ammonium carbamino-stibanilate or urea-p-tibanilate, but it has been shown by the author and his co-workers (1928) that it is not a compound but a loose combination of urea with para-amino-phenyl-stibinic acid. It was found that urea can be completely separated from the compound by repeated washing with alcohol. Besides the variation in the composition of different specimens on the market, even those prepared by the same firm vary enormously. The antimony content shows a variation from 20 to 43 per cent. Urea-stibamine is a brown amorphous powder soluble in water forming a clear yellow solution. Its toxicity is very low. The initial dose is 0.1 gm. increased by 0.05 gm. up to a maximum of 0.25 gm. given twice weekly. The patients quickly develop tolerance to the drug and its action in restoring the normal leucocyte count is rapid and most beneficial. Brahmachari found that blood became negative on culture 34 hours after a single injection in a number of cases and in 73 per cent. the blood became negative in 10 days. The average amount of the drug necessary for the cure of a case is 2.6 gm., the average number of injections is 10 to 12, and days of treatment 32 as compared with 30 to 90 injections and a total period of nearly three months in the case of antimonyl tartrates. The author has successfully treated patients

suffering from kala-azar with daily injections of urea-stibamine for 6 to 8 days, the first dose being 0.25 gm., second 0.3, third and subsequent doses 0.55, a total of 2.5 to 3.0 gm. being given according to the weight of the individual. The duration of treatment has thus been reduced to less than ten days. The earlier a case is treated the more effective the treatment. It is especially useful in those cases resistant to tartrates.

The solution of the drug should not be boiled and the solid drug should not be kept exposed to air.

Stibosan or von Heyden 471. This compound is chemically meta-chlor-para-acetylaminophenylstibiate of sodium. It is a light brown powder, non-hygroscopic and does not decompose in an ordinary corked bottle at room temperature. It is readily soluble in distilled water and forms a sterile solution which does not decompose readily. It was first used by Napier (1923) who gave it intravenously in 1 to 5 per cent. solution; the largest dose given intravenously was 0.5 gm., but this produced nausea and vomiting. The smallest dose which caused any symptoms was 0.2 gm. The solution should be freshly prepared and should not be heated. Generally 10 injections suffice to bring about a cure, beginning with 0.2 gm. for the first dose and 0.3 gm. for subsequent doses given on alternate days. An exceptionally weak individual should be given a starting dose of not more than 0.05 gm.; children tolerate large doses and for a child of nine years 0.2 gm. can be prescribed. The routine course is 11 to 15 injections given 2 to 3 times a week over a period of 3 to 4 weeks; 3 to 4 gm. are sufficient to effect a cure. In every case improvement is uniform and rapid and most of the unpleasant symptoms associated with injections of tartrates are absent. Stibosan is a definite compound and therefore it does not vary in composition. It does not decompose in the presence of air and it is not necessary to open a capsule every time the drug has to be given. It is contra-indicated in cases complicated with ascites but it can be given even if there is albumen in the urine, diarrhoea and chest complications. Jaundice is a contra-indication to its use.

Stibamine glucoside or Neostam. It was prepared by Henry of the Wellcome Research Laboratory. Napier (1925) treated 10 cases with this drug with good results. The compound is easily soluble in distilled water making a 4 per cent. solution and is injected intravenously in doses of 0.05 to 0.3 gm. An initial dose of 0.1 gm. and a maximum dose of 0.2 gm. are satisfactory dosage for patients of average weight. The injections are given on alternate days. The total curative dose is 2 to 3 gm.

Von Heyden 693 is diethylamine para-aminophenylstibinate. Napier tried neo-stibosan in a series of 61 cases without any deaths; fifty were cured, 2 failed to respond to treatment; the mean dose was 3.35 gm. per 100 lbs. body weight. It gave the lowest death rate and proved to

be superior to most of the pentavalent compounds now used. Ten injections produce a complete cure, the total quantity required being 3 to 4 gm. This is a stable compound and has good keeping properties. The anaphylactoid symptoms as well as jaundice are less common with this drug. There were no disagreeable symptoms, with the exception of vomiting.

Neostibosan or Bayer 693B is of the same composition as above but prepared differently; it was introduced to avoid vomiting. This compound forms an isotonic solution in 25 per cent. concentration and can be given effectively by the intramuscular route; 0.3 gm. can be given by daily injection and 8 injections, *i.e.*, a total of 2.4 gm. suffice to cure the disease. There is entire absence of nausea and vomiting and the patients tolerate the maximum dose from the very first injection.

Amino-stiburea. Chemically it is p-aminophenylstibinic acid combined with urea and glucose. The addition of glucose is said to add to the stability and to the diffusibility of the drug. This compound is quite effective against leishmaniasis. The total quantity required to produce a cure was 3.35 gm. per 100 lbs., that is, about the same as other pentavalent aromatic compounds.

Relative value of pentavalent compounds in the treatment of kala-azar. The sterilising dose per kilo. body weight of patients according to Greig and Kundu (1925) works out to be 0.054 and 0.06 gm. for urea-stibamine and stibosan respectively; the curative value is about the same. The number of injections in the case of all pentavalent compounds was nearly equal but was lowest with neostibosan. The average number of injections before the fever subsided was as follows:—Stibosan (No. 471) 5.6, satibamin glucoside 5.4; urea-stibamine 5.1; neo-stibosan (No. 693) 4.57; aminostiburea 4.48. Stibosan and neostibosan are the most stable compounds. Neostibosan is the most innocuous and produces a cure in the shortest period; it gives the lowest death rate during treatment. Patients can now be cured with a routine treatment of eight daily injections of 0.3 gm. of neostibosan.

The course of the disease under treatment. The fever usually subsides after the fifth injection, or even earlier but it may persist for a fortnight or more. In most cases the downward tendency of the temperature is immediately apparent, in some cases the temperature remains at about 100°F throughout the course of injections, only coming to normal when the course is discontinued. In some patients a reactionary rise

after each injection is observed. A sudden sharp reaction means that the dose has been too big.

The general condition of the patient begins to improve soon after the injections are started; the weight may decrease slightly at first but then rapidly increases during the course. The hair ceases to fall out and regains its normal lustre; the appetite improves and there is a sense of well-being. In women menstruation usually begins when the course of treatment is ended. The spleen diminishes rapidly in size and in most cases disappears below the costal margin at the conclusion of the treatment. In some patients the effect on the spleen is slower and in others it is only appreciable when the course of injections is nearing completion. The behaviour of the spleen is dependent on its consistency; when it is fibrous and hard, diminution beyond a certain limit is not possible. The liver seldom shows any tendency to decrease until after the injections have been completed.

The blood picture improves rapidly and by the time the course is completed the leucocyte count is normal or may even indicate leucocytosis; there is a noticeable increase in the eosinophiles; the erythrocyte count also shows an increase.

No dose, however large, can be guaranteed to produce a 100 per cent. cure rate. A spleen or liver puncture gives the best indication of cure but it should be remembered that the effect of antimony continues for some time after the last injection. This is shown by the fact that patients who show Leishman-donovan bodies on spleen or liver puncture become entirely negative some weeks later. The best plan is to give a full course of injections and if there is a relapse a more intensive second course should be started.

Relapses. If the full amount of the drug has been given relapses are not very common; they are only frequent after insufficient treatment. There is no evidence to show that patients who have had previous injections of antimony require much bigger doses to eradicate the disease in the event of a relapse, but the disease in some cases is much more resistant and these require larger doses. When a relapse occurs the patient should be given a much more thorough course of treatment. A

definite enlargement of the spleen usually accompanies a real relapse as distinguished from other forms of fever. In relapses after antimonyl tartrates one of the pentavalent compounds should be tried.

Antimony fastness of leishmania. It has already been stated that trypanosomes may be rendered resistant to antimony though not to the same extent as to arsenic. The same possibility exists in relation to the treatment of kala-azar. It is recommended that the doses of the antimony compounds should be increased and intervals between injections made longer when this condition is developed.

Antimony in pregnancy. Antimony compounds in therapeutic doses have no marked effects on the gravid uterus. Treatment therefore should not be withheld in any stage of pregnancy. Many pregnant women treated with antimony go on to full term and give birth to healthy children.

The evidence of cure. The best evidence of cure is the absence of all symptoms of the disease during at least six months following the course of treatment. It has been shown that even though cultures from the spleen and liver puncture are positive weeks or months after the completion of treatment the patient may still attain a cure.

A number of tests introduced recently for the diagnosis of kala-azar may be employed as evidence that cure has been effected.

1. **Napier's aldehyde reaction.** This test consists of adding one drop of 40 per cent. formaldehyde to 1.0 c.cm. of serum in a test tube. The mixture is then shaken and allowed to stand at room temperature. Within 3 to 20 minutes the serum becomes absolutely solid and opaque. This test is positive in 83.5 per cent. of cases. When the patient is cured this test becomes negative.

2. **Chopra's antimony test (Serum test).** Whole serum and serum diluted 1 in 10 with distilled water are put in miniature test tubes (2½ to 3 inches long made by sealing one end of a piece of glass tubing 4 to 5 mm. in diameter) with a capillary pipette. A 4 per cent. solution of urea-stibamine

made with distilled water is then slowly run along the side of the tubes. A heavy coarsely-flocculent precipitate forms when the antimony solution comes in contact with the serum. Tartar emetic does not give this reaction but stibosan does. During treatment with pentavalent antimony compounds the test becomes uncertain at first and then, after the full course of treatment, it is negative. In very early cases 1 in 10 dilution of the serum may give negative results and whole serum should be employed. A correct diagnosis can be made by this test in 88.2 per cent. of cases as compared with 83.5 per cent. of the aldehyde test.

Finger prick blood test. A drop of blood from the cleaned finger is received into a small test tube ($\frac{3}{8}$ inch internal diameter and 2 inches long) containing 0.25 c.cm. of a 2 per cent. solution of potassium oxalate. The corpuscles are allowed to settle down and the test is performed with the supernatant fluid. A 4 per cent. solution of urca-stibamine is added in exactly the same way as in the serum test. A flocculent precipitate means a positive test. The reading should be taken from 5 to 10 minutes after mixing the solution. A positive test is obtained in 86.4 per cent. of cases. Both these tests become negative when the patient is cured.

(3) **Lloyd and Paul's test.** In normal serum there is on the average 0.16 gm. of euglobulin per 100 c.cm. of serum or approximately 5 per cent. of total globulin; in well-established cases of kala-azar it is 1.5 to 2.5 gm. per 100 c.cm., i.e., 40 to 50 per cent. of the total globulin. Lloyd, Napier and Paul applied the method of protein graphs to estimate the cure of kala-azar after treatment with antimony compounds. The protein fraction estimations are made by the refractometric method described by Robertson (1924). There is a steady ascent of the pseudo-globulin and a steady descent of euglobulin, and finally euglobulin attains the normal figure of approximately 0.16 gm. per 100 c.cm. of serum when there is complete cure. The graphs give an index of the condition of the disease. It is suggested that high globulin content of serum in kala-azar is an immunity response and such cases react to treatment

rapidly, while the low protein type of case with a weak aldehyde test represents the opposite condition.

(4) **Chopra and Choudhury's test.** By noting the time of gelation with formalin of the sera from the blood of kala-azar patients, it is possible to indicate in a general way, the progress towards cure. Information regarding progress towards cure may be said to be satisfactory, if the time of gelation is more than half an hour. If however the time of gelation before treatment is known, and this can be easily determined from an aldehyde test, the corresponding increase of the time of gel formation also gives useful information.

Antimony in Other Affections

Syphilis. Niesser was the first to suggest the employment of antimony compounds in the treatment of syphilis. Monkeys can be rendered immune by injecting organic compounds of antimony but metallic antimony and antimonyl tartrates of sodium and potassium are less effective. The curative effects of antimony preparations in syphilis in rabbits has been studied. After tartar emetic in doses of 0.01 gm. per kilo. intravenously, the lesions showed only non-motile spirochaetes the following day, but active organisms were again found on the third day. On the whole, it appears that antimony possesses but a feeble toxic action against the spirochaetes. Syphilis in man has been treated with injections of tartar emetic (1 in 1,000) and although it improves certain manifestations, it does not appear to have any marked effect on the progress of the disease.

Framboesia. Injections of antimonyl tartrates have been tried in jaws, but there was no marked effect even after 8 to 10 injections.

Malaria. Rogers originally suggested the use of antimonyl tartrates in the treatment of malaria. It was at first thought that injections of these compounds destroyed the asexual parasites as well as the sexual forms which were unaffected by quinine. Further work showed that the tartrates or the organic compounds have little or no action on the malarial parasites.

Granuloma inguinale is a disease endemic in many tropical countries. It was thought to be produced by an organism which was first described by Donovan, and believed by some to be a protozoon and which recent work has demonstrated to be a non-motile capsulated bacterium of the rhinoscleroma group called *Calymatobacterium granulomatis*. This organism however has not been definitely proved to be the cause of the disease. Injections of antimonyl tartrates as well as thio-glycollate of antimony have given good results in this condition.

Antimony in helminthic infections (see Helminthic Diseases).

Rat-bite fever. Injections of stibosan have been tried in this condition with beneficial effect. Neither tartar emetic nor stibenyl produces any effect.

Trypanosomiasis. Antimonyl tartrates have a remarkable effect in diseases produced by trypanosomes in animals. It was found that 1 mgm. of antimony caused immediate disappearance of the parasites in rats weighing 200 gm. Plummer and Thomson (1908) noticed the sterilising effects of potassium and sodium antimonyl tartrates in laboratory animals infected with *T. brucei*, and *T. evansi*. Rats inoculated with nagana died in an average time of 5 to 6 days; if on the fourth day, when the blood was full of parasites, 5 mgm. of tartar emetic were injected subcutaneously the parasites were killed, the rats usually survived and some recovered completely; relapses, however, not infrequently occurred. Arsenic and some aniline dyes produce the same type of effect but are inferior to antimony compounds in this respect. Triamide of antimony thioglycollic acid was found to be quite effective against *T. brucei*, *T. evansi*, and *T. equiperdum* in rats, dogs and rabbits. Antimony triamide in 30 per cent. suspension in oil was tried intramuscularly with success in trypanosome infections, including *T. gambiensi*; a large number of other antimony compounds were also tried in the treatment of this infection in animals and rapid disappearance of the parasites after intravenous injections, was observed. The effects were so rapid that there appears to be little doubt that the trypanocidal action is due to antimony and not to the formation of antibodies. No evidence of agglutination or phagocytosis has been found; the parasites are first rendered incapable of multiplication and then rapidly die. The trivalent compounds are much more effective in this respect than pentavalent compounds. Nothing is known regarding the immunological factors in relation to the trypanocidal activity of the antimonyl compounds, but Kolmer is of opinion that in animals successfully treated, a period of immunity follows.

Antimony compounds were first tried in the treatment of human trypanosomiasis many years ago. Borden (1910) successfully treated sleeping sickness in the Congo with injections of tartar emetic. Kerandel successfully treated himself with injections of tartar emetic after failing with atoxyl. Owing to the chronicity of the disease, and the great tendency to relapse after long intervals of absence of the parasites from the peripheral circulation, it is very difficult to draw any conclusion regarding the curative effects of the drug. The successful treatment of trypanosomiasis entails strict control over the patient, possibly for two years. Moreover, the stage

at which the treatment is adopted is an important factor to be taken into consideration. If the cerebrospinal system is affected no form of treatment will check the almost inevitable steady progress towards a fatal termination. Another difficulty is that the treatment has to be protracted because as much as 500 grains of tartar emetic are required to destroy the trypanosomes. The administration of such large quantities may take a year or more, and this affords the parasite the opportunity of permanently damaging the nervous tissues. Intravenous injections of antimonyl tartrates of potassium and sodium are undoubtedly worthy of trial in this disease; the pentavalent aromatic compounds of antimony have not proved effective in this condition. Preparations containing azo-dyes and antimony have been tested on laboratory animals but results are not encouraging.

Dermal and muco-cutaneous leishmaniasis. Under this heading are included oriental sore and generalised dermal leishmaniasis, both of which occur in India, and the muco-cutaneous form or *espundia* which occurs in South America. The parasites responsible for these conditions are culturally and morphologically indistinguishable from those of kala-azar. Oriental sore is produced by *L. tropica*, the organism occurring in the thickened edges of the sore. The distribution of oriental sore is in marked contrast to that of kala-azar, as the former occurs only in north-western parts of India, Mesopotamia, and Asia-minor where kala-azar is not met with. Ulcerative conditions commonly occur in dogs in the endemic areas of oriental sore, in Tehran, Algiers, Aleppo, etc. Chronic cutaneous leishmaniasis can be produced by inoculating mice on their tails with a few drops of *L. tropica* cultures. *P. papatasi* is probably the carrier and those flies fed on sores become infected. Direct inoculation at the time of biting rather than the contaminative method through parasites in the flies' excreta, produces infection. *Espundia* has a wide distribution in the tropical portions of South America. The transmission has not been worked out but *P. lutzi* is suspected. The ulceration occurs in oro-pharyngeal mucosa with extensive involvement of the nose and throat; many cases resemble oriental sore. For the dermal infection, which is a sequel of

kala-azar, intravenous injection of antimony compounds is considered by Napier (1927) to be the only treatment and cases in which there was no previous history of kala-azar cleared up rapidly, usually about ten injections being necessary. The cases which have been previously treated for kala-azar are much more resistant and even 5 gm. of stibosan may have no effect.

Oriental sore may heal in 6 to 18 months without treatment and intravenous injections of tartar emetic are regarded as a drastic procedure. If antimony is used the line of treatment is the same as in kala-azar, 10 to 20 injections making a total of 2 to 3 gm. of tartar emetic suffice in most cases. Pentavalent compounds of antimony have also been used with good results. X-rays and antimosan have been considered by some to be very effective. A 2 per cent. ointment of tartar emetic in paraffin and ionization with such ions as zinc, iodine, etc., carbon dioxide snow, methylene-blue ointment, strong solutions of zinc sulphate, powdered potassium permanganate have been administered and are sometimes successful.

Besides antimony other drugs have also been tried in *L. tropica* infection. It has been shown that berberine sulphate in dilutions of 1 in 80,000 inhibits the growths of *L. tropica* and *L. donovani*, while quinine and emetine in 1 in 1,000 dilution have little or no action. One-third of a grain (0.02 gm.) dissolved in 1.5 c.cm. of distilled water is injected round the base of the sore. Injections are given at weekly intervals and solutions must be freshly prepared; after injection a dressing of hypertonic salt solution is applied. Healing takes place in 5 to 14 days as compared with 18 days of tartar emetic treatment. Not more than one or two sores should be treated at one time. Emetine hydrochloride injected locally around the edge of the sore produces healing. Doses of 0.15 grains (0.01 gm.) are given to start with, increased 5 to 10 times according to the size of the sore, and healing takes place in 15 to 30 days. Twenty minims of a 5 per cent. solution injected into the edges make the sores well defined in 3 to 4 days and healing takes place in a short time.

The muco-cutaneous form is more resistant to antimony than infections with *L. donovani*. Injections of Martindale's oxide of antimony, trioxide of antimony as a local application, ointments of stibenyl and stibosan, have all been used with good results. Fouadin intramuscularly is said to heal the lesions rapidly. For adults the doses recommended are 1.5 to 3.5 c.cm. for the first 2 injections, subsequently 5 c.cm. There is no local pain or reaction, 20 to 30 injections may have to be given. Eighty per cent. solution of lactic acid has been found by some to be superior to antimony injections. Stovarsol, Bayer 205, antimosan, iodobismuthate of quinine, amino-arseno-phenol have been tried with varying degrees of success, but no specific treatment has been discovered.

Modes of Administration

By the skin. A five to ten per cent. ointment of metallic antimony in lanoline base was recommended in the treatment of leishmaniasis, one drachm being rubbed over the abdomen every second or third day. It has no appreciable effect on the course of the disease. Oriental sores have been successfully treated with a 2 per cent. ointment of tartar emetic, the application being made at night. The irritant action of tartar emetic when applied to the skin in the form of an ointment is due to its being broken up by the acid formed by decomposition of the sweat. If sodium bicarbonate is added to the ointment the irritating effects are considerably reduced.

By mouth and per rectum. The antimony salts are not suited for administration by the mouth except in very minute quantities. Their irritant action gives rise to emesis and they are not easily absorbed from the alimentary canal. Before the discovery of the pentavalent organic compounds, intravenous injections were supplemented by oral administration of tartar emetic but it was not well borne. This route cannot be adopted when it is necessary to introduce large amounts into the body as in cases of protozoal diseases.

Rectal injections of tartar emetic, urea-stibamine, etc., have been tried; the former salt is too irritating and causes much pain and discomfort. The latter is not so irritating but

the quantity absorbed by this route is too small to produce a concentration in the blood lethal for leishmania.

Subcutaneous and intramuscular methods. Subcutaneous injections always produce cellulitis and abscess formation.

Intramuscular injections even of the double salts are very irritating, not only is severe pain produced but extensive necrosis of tissues at the site of injection occurs. Attempts have been made to discover preparations which can be given this way without harmful effects. Martindale's solution of the oxide in glycerine and water gave variable results. Colloidal sulphide of antimony in suspension, hyperacid antimonyl tartrate, urea-stibamine, and stibacetin, have been tried intramuscularly. Although they do not produce much pain, absorption of antimony is irregular and is not sufficiently large to produce a concentration in the blood, lethal to the parasites. Such compounds as antimosan, fouadin, stibosan and neostibosan administered by the intramuscular route are said to be quite effective. The advantages of this method are that, as compared with the intravenous route, little skill is required; besides, in very young children it is sometimes impossible to get at the veins embedded in the subcutaneous tissue.

Intravenous route. The intravenous method of administration is the only method by which uniform success can be claimed and most of the antimony compounds can be introduced direct into the blood stream with safety. The only objection is that it requires special technical skill, but that can be easily attained with a little practice. It has been asserted that intravenous injections are painful, and some have gone so far as to say that they are dangerous and that one is not justified in using this method, especially in mild diseases like oriental sore. Experience has, however, amply proved that the danger is slight if proper care is taken as regards technique and regulation of dosage of these compounds. The technique of intravenous injection is described in the chapter on intravenous therapy.

CHAPTER XII

COMPOUNDS OF ANTIMONY

Like many metals antimony forms two series of compounds, its valency varying from three to five.

Antimony compounds may be classified as (1) Inorganic salts. (2) Organic salts, e.g., antimonyl tartrates are trivalent compounds. (3) Organic compounds.—(a) Trivalent, these are unstable. (b) Pentavalent, these are stable and are commonly used.

Chemotherapy of antimony compounds. Uhlenhuth and his colleagues (1925) tested antimony compounds on mice infected with dourine, intraperitoneal injections of the compounds being made on the third day after infection. They tested two groups of antimony compounds, and their results, based on one injection in each case, are as follows:—

(1) The first series constitute the phenyl stibinic acid derivatives which are therapeutically active and in which antimony is united directly to carbon. Drugs belonging to this group are stibenyl and stibosan. In this series antimony is pentavalent.

(2) In the emetic series antimony is linked to oxygen and only through oxygen to the carbon. In these compounds antimony is trivalent; antimosan is a member of this group.

In the first series it is recognised that variation in the toxicity and therapeutic activity is possible by substitution of one or more of the hydrogen atoms in position 2 and 6 in the ring, by other atoms or groups such as chlorine (Cl) or amino (NH_2) or hydroxyl (OH) groups. Comparatively slight changes in the structure of these compounds produce considerable differences in their toxicity and therapeutic action. For example, substitution of a chlorine for a hydrogen atom in position 3 changes stibenyl into stibosan while by increasing the toxicity (M.L.D. 5 instead of 12 mgm.) the curative power is also increased, the dose usually being 2 mgm. in the place of 5 mgm.

The replacement of the acetyl-amino-group of stibenyl by chlorine increases, on the contrary, the toxicity and at the same time destroys its trypanocidal action. In the emetic series there are three components, the base potassium, the active element antimony and the acid radicle, tartaric acid. All these components can be and have been varied and in general it has been supposed that no matter how the base and the acid radicles are varied, the toxicity and therapeutic activity are determined solely by the amount of antimony present, though when potassium is replaced by a therapeutically active base such as quinine, there may be additional activity due to the quinine.

It is pointed out that by making the acid radicle a catechol (1-2 dihydroxy-benzene) derivative, definite variation in the action of the antimony becomes possible without further changes in the constitution of the molecule. In addition the products are stable to alkali and can be injected intramuscularly as well as intravenously. Antimosan produced in this way has an M.L.D. of 8 mgm., 1 mgm. causes the disappearance of trypanosomes from dourine-infected mice in three hours but they return in 10 to 15 days; an initial dose of 2 mgm. causes their disappearance without return. Tartar emetic was found to have an M.L.D. of 0.8 to 1.0 mgm. Trypanosomes disappear after a dose of 0.5 mgm. but return in from 13 to 20 days, and with one exception it was not found possible to ensure their complete disappearance. Antimosan has been tried clinically but is found to be less effective than stibosan in kala-azar though good results have been obtained in multiple sclerosis.

1. **The inorganic compounds.** Only a few of these are used in therapeutics. Two sulphides of antimony are well known, the black sulphide or trisulphide Sb_2S_3 and the golden sulphide Sb_2S_5 . Antimony sulphuratum is a mixture of various sulphides and oxides and is an orange-red powder; the dose is 1—2 grains. Antimony forms 3 oxides, (1) antimony trioxide Sb_2O_3 (2) Antimony tetroxide Sb_2O_4 and (3) Antimony pentoxide Sb_2O_5 . Antimony oxide Sb_2O_3 is a heavy white powder and is used in solution in glycerine. Metallic antimony in a fine state of subdivision as an impalpable powder, colloidal antimony and antimony sulphide in a colloidal state have been used by intramuscular injections in leishmaniasis and other protozoal affections, but their therapeutic action is not marked. A 5 per cent. ointment of powdered metallic antimony has been prepared and used.

2. **The organic salts or the trivalent compounds.** Of these antimonium tartratum or 'tartar emetic', which was discovered in 1631, is well known; sodium antimony tartrate is also an old compound. The dose is $\frac{1}{2}$ to 2 grains intravenously usually in 1 or 2 per cent. solution. Hypodermically they are both very irritating. Potassium antimonyl tartrate $[K(SbO)C_4H_4O_6]_2 \cdot H_2O$ occurs in crystals and is soluble in 17 parts of cold water but it is almost insoluble in alcohol. It contains 36.17 per cent. of antimony as compared with 38.01 per cent. which is contained in sodium antimony tartrate and 36.51 per cent. in the ammonium antimony tartrate.

Sodium antimonyl tartrate was originally tried by Thomson, who was struck by its effect on trypanosomes. Rogers' experiments on pigeons and rabbits showed that the sodium salt is less toxic than tartar emetic and also the local irritant effects are less marked. The properties, therapeutic and other effects of this compound are the same as 'tartar emetic'. It is also known by the name of 'stibinol'.

An alkaline solution of sodium antimony tartrate known under the name of 'neostibinol', is said to be less toxic but equally efficient.

Antimony aniline tartrate occurs in white crystals and is soluble in 7 parts of water. It is claimed to have a low toxicity after hypodermic injections and is said to possess a considerable activity against trypanosomes. Sulphoform or triphenyl-antimonii-sulphide has been used in skin diseases, antimony thioglycollamide and antimony sodium thioglycollate have been prepared and have proved effective against experimental trypanosomiasis in rats, dogs and rabbits.

3. Aromatic compounds of antimony. (a) *Trivalent.* A large number of antimony analogues of the organic arsenicals have been prepared. The trivalent compounds, i.e., the analogues of salvarsan, are not only difficult to prepare, but also are less stable and not easy to purify. None of them fulfil any of the conditions necessary for an efficient trypanocide. These are : firstly, the compound must be non-irritant and capable of forming a perfect solution at the temperature of the body and at the alkalinity of the tissues; secondly, it should act as a parasiticide quickly, so that there is not sufficient time for tolerance to be developed; and thirdly, when the parasites have once been expelled from the blood there should be no recurrence in the majority of cases. None of these compounds have been found to satisfy these conditions.

(b) *Pentavalent.* The origin of the aromatic antimonials is due to the work of Michaelis and Reese whose investigations led to the preparation of triarylstibines. Later, Grignard's reaction gave rise to the preparation of triphenyl-stibamines. The present development of the organic antimony derivatives is, however, mostly due to the work done by Professor Schmidt of Chemische Fabrik von Heyden who discovered the process of introducing into the aromatic nucleus the antimonial group, through the agency of the diazo-reaction. Great impetus was thus given to the synthesis of aromatic antimonial drugs and most of the antimony analogues of the aromatic arsenical drugs such as atoxyl, salvarsan, etc., were prepared. From aniline by diazo-synthesis it was quite easy to prepare phenyl-stibinic acid and then para-amino-phenyl-stibinic acid (p-stibanilic acid), which is the antimony analogue of p-arsanilic acid. Its sodium salt, sodium para-amino-phenyl-stibinate (or sodium-stibanilate) is the antimony analogue of the arsenical compound known as 'atoxyl' or 'arsamin' (sodium p-arsanilate). This compound was later given the name of *stibamine* by Brahmachari from its analogy to the corresponding salt of arsenic which is called *arsamin*. A derivative of this, sodium acetyl-p-amino-phenyl stibinate, was called 'stibacetin' which was one of the earlier members of the aromatic series to be used in the treatment of leishmaniasis under the name of stihenyl. This compound is soluble in water, it is stable and does not irritate the tissues to the same extent as do some of the organic antimony compounds, so that it can be given intravenously as well as intramuscularly.

Unfortunately, however, it has not proved of any great therapeutic value in kala-azar in this country.

The sodium salt of p-amino-phenyl-stibinic acid, or sodium p-amino-phenyl-stibinate (stibamine of Brahmachari) is also a soluble compound which, though therapeutically active, is unfortunately not very stable. Its therapeutic application is therefore limited. Brahmachari (1925) prepared the carbamide derivative of p-amino-phenyl stibinic acid by warming p-amino-phenyl-stibinic acid suspension in water and urea until the acid is almost dissolved; this is concentrated on a water-bath and the salt is precipitated by the addition of alcohol. The resultant substance, urea stibanilate or ammonium carbanilino-stibanilate, was called 'urea-stibamine.' This substance is a pentavalent compound of antimony and Brahmachari believes it to be a substituted urea and not a urea salt of stibinic acid. The constitutional formula given by Brahmachari has however been doubted and criticised. This compound has also been prepared and sold under the name of stiburea, urea-stibol, stiburamin.

The combination of urea with p-amino-phenyl-stibinic acid renders the latter compound more stable and soluble (p-amino-phenyl-stibinic acid is not soluble) and at the same time, it is more efficacious therapeutically. It is a well-known fact that when quinine is combined with urea, its solubility and diffusibility are considerably increased, and the resultant compound is able to penetrate better into the tissues; its local anæsthetic action is also much enhanced. Similarly, better penetrability of these compounds probably accounts for the superior therapeutic results obtained by them as compared with the previous compounds.

Von Heyden a few years ago, introduced a compound, metachloro-para-acetyl-amino-phenyl-stibinate of sodium (chloro-stibacetin or von Heyden 471) under the trade name of 'stibosan'. The same firm later introduced two other compounds diethylamine-para-amino-phenyl-stibinate (von Heyden 693) and neostibosan (von Heyden 693 B). Both these compounds were tried by Napier (1923 and 1927) and gave very good results in the treatment of kala-azar. They are much more efficacious than some of the earlier organic aromatic compounds of antimony such as stibenyl and are at least as effective, if not more, than urea-stibamine.

Stibamine has also been combined with glucose and a preparation 'stibamine glucoside' also known as 'neostam' is on the market. A number of other organic antimony compounds are available and some of them have been tried with success in the treatment of kala-azar. One of these compounds is p-amino-phenyl-stibinic acid combined with urea and glucose, which has been prepared by a Calcutta firm and sold under the trade name of 'amino-stiburea'. Most of the antimony compounds in use at present are not very stable in the air, even in a solid condition and in solution some of them change very rapidly.

The following table briefly gives the modes of administration and therapeutic effects of various pentavalent compounds of antimony.

Pentavalent Compounds of Antimony

Nature of compound.	Trade name.	Makers.	Remarks.
Salts of para-amino phenyl-stibinic acid. Sodium p-amino-phenyl-stibinate or sodium stibanilate.	'Stibamine'	von Heyden.	Not stable and therefore not used.
Diethylamine para-amino-phenyl-stibinate.	No. 693 & 693 B. Neostibosan.	von Heyden. Bayer Meister Lucius.	Very effective in kala-azar.
Derivatives obtained by substitutions in the amino-groups of para-amino-phenylstibinic acid.	Urea-stibamine Stiburea. Urea-stibol.	Brahmachari.	An effective remedy against kala-azar.
Urea combined with p-amino-phenyl stibinic acid (ammonium para-carbamyl-amino-phenyl stibinate.)	Stiburamine.	B.C.P.W.	
Acetyl-p-amino-phenyl stibinate of sodium. Nitrogen glucoside of sodium p-amino-phenyl-stibinate. Para-amino-phenyl-stibinic acid combined with urea and glucose.	Stibenyl. Stibacetin. Stibamine glucoside. Neostam. Aminostiburea	von Heyden Burroughs Wellcome & Co. Union Drug Co., Calcutta.	Tried in kala-azar but less satisfactory.
Derivatives obtained by substitutions in the benzene nucleus of para-amino-phenylstibinic or para-acetyl amino phenylstibinic acid.			
Mcta-chlor-para-acetyl-amino-phenyl stibinate	No. 471 Stibosan.	von Heyden.	Effective, but now superseded by Neostibosan.

Table of Toxicity of Antimony Compounds

Name.	Minimum lethal dose in mgm. per kilo. of mice.	Maximum tolerated dose in mgm. per kilo. of mice.	Percentage of antimony.
Potassium antimony tartrate ...	16
Sodium antimony tartrate ...	20
Stibacetin and stibenyl ...	133	...	33
Urea-stibamine, Stiburea, Ureastibol	250	175	20—43
Stibosan or von Heyden 471 ..	275	200	31
Stibamine glucoside. Neostam ...	500	300	30
Aminostiburea	250	...	24.8
Von Heyden 693 & 693 B. Neostibosan	350	250	40

The pentavalent compounds can now be therapeutically tested on the striped Chinese hamster *Cricetulus griseus* or the European hamster *Cricetulus frumentarius* both of which can be easily infected with leishmania. The chemotherapeutic index of some of the compounds is as follows:—

Antimosan 1: 5, Stibosan 1: 5 to 1: 7 and Neostibosan 1: 50

CHAPTER XIII

TOXIC EFFECTS

A. Complications due to antimonyl tartrate injections

Certain toxic symptoms follow injection of antimonyl tartrates. Of all the symptoms according to Christopherson (1921) cough, metallic taste and a feeling of tightness in the chest are most frequent. Cough, retching and colic indicate a need for caution. Jaundice and a larger amount of albumin in the urine than can be accounted for by the disease are signs of danger. So far as is known acute toxic reactions of the 'nitritoid crisis' type do not occur with antimonyl tartrates. The toxic symptoms that are produced may be grouped as follows:—

1. **Gastro-intestinal and respiratory.** Severe coughing may occur immediately after the injection and may be so severe as to end in vomiting. It is an indication that the dose has been excessive and should not be increased. After a large dose the patient may vomit 5 or 6 times. By decreasing the dose and then gradually increasing it, a certain degree of tolerance can be established. Both coughing and vomiting may be induced by giving the injection on a full stomach or by giving it rapidly. In some cases a violent fit of coughing has followed even the smallest doses and recurs with each injection. Delayed vomiting may start 4 to 5 hours after injection, acute diarrhoea may sometimes follow, a metallic taste may be noticed after injection. Codeine $\frac{1}{2}$ grain or a few minims of adrenalin given a quarter of an hour before the injection will reduce the tendency to vomiting. Pneumonia and lung complications occur frequently with antimonyl tartrates but they are extremely rare with the pentavalent compounds. If a very large dose is rapidly given the respiration may stop.

2. **Cardiac symptoms.** These consist of cyanosis, rapid and irregular pulse, a choking feeling in the chest and tachycardia. Marked slowing of the heart has occasionally

been noticed towards the end of the course. During the injection there is hardly any fall of blood pressure.

3. **Cerebral symptoms.** These are said to occur more commonly during treatment of trypanosomiasis. Loss of consciousness with incontinence of urine and fæces may sometimes ensue. Severe headache or hemicrania has been observed after 6 to 9 injections and it does not clear up till the injections are discontinued.

4. **Arthritic symptoms.** Severe joint and muscular pains frequently occur but are less common towards the end of the course. Pain in one or both shoulders, and lumbago are common complications; the wrist joint, knee joint and ankle joint may be affected and the pain may last for some time. Usually the joint pains commence 4 to 6 hours after an injection, generally after a total of about 10 grains of antimony tartrate and they last for about 12 hours. Ten grains of aspirin given half an hour before the pains are expected to begin, diminish their severity. Codeine in $\frac{1}{2}$ -to 1 grain doses counteract most of these symptoms.

5. **Other symptoms.** An irritating papular eruption of the skin may occur on any part of the body. A sharp rise of temperature with rigor is generally due to injection of faulty solution. Profuse sweating or fainting is of rare occurrence.

B. Complications after injections of pentavalent compounds.

The fit of coughing which not infrequently occurs after injection of antimonyl tartrates does not, as a rule, occur with the organic aromatic compounds. Nausea and vomiting are seen in about 10 per cent. of cases, but rarely with neostibosan (von Heyden 693 B) except when the dose is very large. If nausea and vomiting persist the dose should be reduced. The tendency to vomiting can often be overcome if the dose is increased very gradually. After injections of stibosan vomiting not infrequently occurs, and this is a serious drawback. Generally the vomiting begins within 20 minutes of the injection and it may be preceded by giddiness. If the patient remains quiet in bed vomiting may be avoided. The injections should

not be given immediately after a meal. Diarrhoea may occasionally occur towards the end of the course and may be severe. The motions are dark, watery and frequent; they contain no blood or mucus. Fatal collapse and death are on record. A severe attack of shivering lasting for 2 hours may be the only feature. Cardiac, cerebral and arthritic symptoms have not been noticed.

Symptoms of an anaphylactoid nature resembling the 'nitritoid crisis' (occurring with organic arsenicals) sometimes develop. 'This is to be expected as both these series of compounds are of semi-colloidal nature and give rise to changes in the blood; they also produce an enormous rise of pulmonary pressure. These symptoms set in suddenly after the sixth or seventh injection, when the patient has been receiving maximum doses. Within a few minutes of injection the face becomes puffy, the voice husky, there may be an urticarial rash on the body, dyspnoea and stertorous breathing. The patient has a feeling of impending death. The pulse becomes weak and imperceptible, the patient is cyanosed and coma and collapse may soon supervene. The condition though alarming, is rarely fatal and as a rule all symptoms disappear in two hours; puffiness of the face may last for 24 hours. In Napier's series, these symptoms were more frequently observed with aminostiburea and urea-stibamine and were rare with neostibosan. Injections of a few minims of adrenalin or pituitrin relieve the symptoms. If these symptoms occur it is best to abandon treatment with a particular compound, recommencing it with minute doses of some other compound.

It has already been pointed out that agglutination and hæmolysis of red blood corpuscles do not occur even with concentrated solutions of the antimony compounds. These symptoms therefore cannot be due to embolism of the capillaries of the lungs and other organs. Chopra and his associates (1927) have shown that when organic antimony compounds come in contact with the serum of kala-azar patients a thick flocculent precipitate is formed; this precipitate is not produced with non-kala-azar serum and this reaction has been used as a diagnostic test for the disease. It is possible that some of

the untoward symptoms produced may be due to this precipitation.

Rarely, acute congestion of liver or even symptoms of acute hepatitis are produced by injection of these compounds. The liver becomes enlarged, tender and painful ; the temperature rises and there may be jaundice. The symptoms disappear if the injections are stopped and are apparently due to the toxic action of the compounds on this organ. Jaundice may sometimes appear 1 to 3 months after the course. Dermatitis of an exfoliative nature has not been noticed.

Choice of a compound. The chief factors to be taken into account in the selection of a compound are the toxic effects produced, the time necessary to produce a cure, the ease of administration and the relapse rate after treatment. Anaphylactic symptoms are common with urea-stibamine and amino-stiburea, but are rare with stibosan and neostibosan. The relapse rate is also lower with the latter compounds and they are more stable. Neostibosan is the easiest to administer as it can be given intramuscularly in doses of 0.1 gm. to 0.3 gm. without causing pain and it is effective. Both these compounds are, however, expensive. Urea-stibamine and allied compounds are nearly as effective and are slightly cheaper.

Cumulative action. Cautions and contra-indications. The human body can stand large doses of antimony especially when it is given intravenously. The reason for this is that when administered by this route large quantities are eliminated from the system by the kidneys.

Antimony salts should be employed with great caution in weak, anæmic and emaciated subjects. If disease of the heart, kidneys or lungs co-exists special care should be taken. Before starting the injection and during the course of treatment the urine should be examined frequently for the presence of albumin.

CHAPTER XIV

MODE OF ACTION OF ANTIMONY COMPOUNDS

The mechanism of curative action of antimony compounds in leishmaniasis and bilharziasis is not understood. The important factor in the treatment of all protozoal diseases is that when an attempt is made to exterminate these parasites in the tissues, what appears to take place is that the drug destroys the majority of the parasites. The body resistance then rises and the patient's own natural powers of resistance finally eradicate the residual infection. This is almost certainly the case in kala-azar, where not infrequently a patient at the conclusion of a course of treatment may still show a few leishmania in the film on spleen puncture, and yet remain in perfect health thereafter and be cured. The same appears to hold good for malaria and trypanosomiasis and probably for amebiasis also.

In vitro experiments show that tartar emetic has little action on the cultures of leishmania. The toxic effects are not increased by bringing it in contact with fresh animal tissues; the organic arsenicals such as salvarsan, neosalvarsan, etc., are ten times more lethal to leishmania *in vitro* and yet they are not effective in the disease. Antimony is evenly distributed in the body and is quickly excreted by the kidneys; it never attains such a high concentration as may be directly parasiticial. The pentavalent compounds do not differ in this respect from the trivalent compounds, and after an injection most of the antimony is, as a rule, eliminated in 3 or 4 days. Vogtline and Smith (1920) consider that pentavalent organic antimony compounds are first reduced to the trivalent state before they become active. It is very probable that the antimony ion in some form constitutes the parasiticial agent, but whether oxidation or reduction occurs forming new compounds, or whether some protein compounds are formed in the serum, is difficult to say. The mechanism appears to be very similar to that of the action of mercury on the spirochaetes and it is probable that

antimony ions act by direct combination with the protoplasm of the parasites for which they appear to have a special affinity. The readiness with which antimony compounds dissociate into antimony ions is an important factor in their parasitotropic and organotropic properties. In mice infected with dourine, tartar emetic rapidly destroys the trypanosomes, since they disappear from the peripheral blood stream in 2 or 3 hours after the injection. With the pentavalent compounds, there is an interval of from one to two days before the trypanosomes disappear; but whether this latent period is due to a gradual reduction to a trivalent compound is not known. In human kala-azar there is also an interval which suggests that antimony in some way stimulates certain body functions, rendering the body environment detrimental for the development of leishmania. Chopra and Das Gupta (1927) showed that pentavalent compounds given intravenously stimulate the rhythmic contractions of the spleen and the liver and free Leishman-donovan bodies are found in the peripheral blood liberated by the rupture of endothelial cells. If the action of antimony was merely stimulatory better results would be obtained by repeated small doses. Clinical experience, however, shows that best results are obtained by pushing the treatment to the point of physiological limits.

Whatever may be the exact mode of action there is no doubt that the death rate in kala-azar has been reduced from 90 per cent. to 5 per cent. and that in Assam and Bengal, on account of extensive use of the antimonials, the disease is no longer in epidemic form and may in time completely disappear. Kolmer is of opinion that specific parasitocidal effects are enhanced or aided by certain non-specific protein reactions commonly observed after intravenous injections of proteins as well as after some metals in colloidal suspension. This is shown by the fact that slight leucocytosis is always noticed in rabbits after injection of antimony compounds, but whether any antibody is formed is not known.

CHAPTER XV

REMEDIES USED AGAINST TRYPANOSOMIASIS

Trypanosomiasis is a chronic disease of endemic areas in Central Africa due to *T. gambiense* or to *T. rhodesiense*, which are transmitted by the tse-tse fly. In man there are two stages of the disease. The first or hæmic stage and the second or the cerebral stage (sleeping sickness). The incubation period varies between two and twelve weeks and probably averages about six weeks. Trypanosomiasis is a very fatal disease. Although spontaneous recovery may take place in the early stages, it is believed that when the disease has arrived at the stage of sleeping sickness death is inevitable. Many areas in Africa have been completely depopulated through the ravages of the disease.

The causative organism. The trypanosomes are blood parasites which are widely distributed in animals, especially in big game in the countries in which these diseases occur. These animal hosts act as reservoirs of the trypanosomes which cause disease in man. *T. gambiense*, as seen in fresh blood, is an active wriggling organism, having a spindle-shaped body which is slightly compressed laterally and spirally twisted. There is no uniformity in the number of parasites present in the blood; sometimes they are fairly abundant, at other times, and in the same patient, it may be difficult or impossible, even after prolonged search, to find a single organism. In some instances they tend to recur cyclically at intervals of a week or more. On the whole, the parasites are most abundant in the blood during febrile attacks. At other times, trypanosomes may be found after triple centrifugalisation of citrated blood. The organisms are also found in the enlarged lymphatic glands, and in the cerebro-spinal fluid, as well as in that of the serous cavities.

Like the organisms of kala-azar, these parasites may be cultured on N. N. N. medium. They can usually be inoculated into most mammals including all the ordinary domestic and laboratory animals.

Germanin or Bayer 205 is a complex organic combination which was prepared in Germany in 1920; when used in veterinary medicine it is called *Naganol*. Its chemical composition was not revealed, but Fourneau (1923) prepared a substance of apparently identical action, named *Fourneau 309*

or *Moranyl*. This compound is believed to be identical with the German product. It is a derivative of the trypan-red class of dyes and chemically it is a symmetrical ureide of m-aminobenzoyl-m-amino-p-tolyl-l-naphthylamine-4 : 6 : 8-trisulphonate of sodium.

Germanin is a fine, white, flocculent powder which dissolves easily in physiological saline and cold water. The solution is faintly pink, odourless, slightly bitter in taste and neutral to litmus. The drug can be sterilised by heating in a water bath for 15 minutes, but solution in sterile water renders this unnecessary. Solutions can keep for some length of time, but it is advisable to give freshly prepared solutions. The drug both in a pure state and in solution should be kept away from light in amber-coloured bottles. A 10 per cent. solution is injected intravenously in man, and it is also said to be well borne subcutaneously, intramuscularly and orally. The intravenous route is preferable.

Pharmacology. Little is known about the pharmacology of this drug. It is slowly absorbed from the alimentary tract. In animals the drug has been found remarkably non-poisonous. The *dosis tolerata* has been estimated to be 160 times that of the *dosis therapeutica*. It could be given intrathecally to a dog in doses of 0.7 gm. without producing irritation or other ill effects. The drug is said to circulate in the blood for some time without losing its efficacy. It probably combines with the proteins of the serum and in this way is fixed and retained. Its presence can be detected in the internal organs for as long as 5 months after treatment. As the drug circulates in the body for weeks or months, it is not necessary to repeat it too often; it is doubtful if better results can be obtained by doing so. The trypanosomes develop a certain amount of resistance to it and it has toxic effects on the host. Its action on trypanosomes is said to be inhibitory to the multiplication of the parasites.

Effects on trypanosomes. It was found that the drug cured mice, rats, guinea-pigs and rabbits infected with *Trypanosoma brucei*, *T. equiperdum*, *T. equinum*, *T. gambiense* and *T. rhodesiense*. A dose of 0.0006 gm. or about 0.0024 gm. per kilogram of body weight cured mice, which become immune to reinoculation for a period of about three months. *T. cruzi* was unaffected but *T. venezuelense* (*T. evansi*) rapidly disappeared from the blood stream. Infections due to *Babesia mutans* or *B. bigemina* were unaffected. The proportion of the effective to the toxic dose (i.e., the therapeutic index) in mice is 1 to 60, whilst in the case of atoxyl it is 1 : 2 (which means that twice the

effective dose would prove toxic). Fifty gm. given by the mouth to a goat, cured infection due to *T. rhodesiense*.

Toxicology. Duncan and Manson-Bahr (1923) found that in mice the drug in the kidneys produced extensive degeneration and exfoliation of the epithelium of the convoluted and other secreting tubules of the cortex; the straight tubules and excretory ducts appeared unaffected; some of the tubules contained hyaline casts and there were necrotic foci. The blood vessels were engorged, minute hæmorrhages occurred in the cortex and vessels showed perivascular round-cell infiltration. The liver and the lungs were engorged and fatty changes and focal necrosis occurred in the former; minute hæmorrhages also occurred in the lungs and in the brain. Marked anæmia was produced. In experiments in which the object is to produce sterilisation after a single dose, a great leucocytic reaction may be observed in relation to the sudden disappearance of parasites and death may result from shock. The drug circulates in the blood for days and even months, and consequently repeated doses have a cumulative effect. Regular examination of the urine is necessary and the appearance of a considerable amount of albumin is an indication to stop the treatment.

Therapeutic uses. Bayer 205 has been tried in sleeping sickness with encouraging results. The drug was given in human patients as early as 1922 with varying effects, the routine treatment being 1.0 gm. of the drug intravenously on the first, third and fifteenth days. In all cases in the first and second stages of the disease the improvement was well marked, but 96 cases out of a total of 150 whose blood was examined weekly, showed relapse. Trials by other workers also show that the first hopes entertained regarding the curative value of the drug were not fulfilled and Bayer 205 is distinctly less effective in trypanosomiasis when it has reached the second stage. Nevertheless, early cases due to *T. gambiense* respond so effectively to the action of the drug, as to suggest a permanent cure. Cases of chronic trypanosomiasis with changes in the cerebrospinal fluid show, as a rule, slight and only transient improvement. In some cases the cerebro-spinal fluid improves several months after the treatment is stopped and the condition may remain stationary. In the majority of cases the disease progresses to a fatal termination. In those cases in which the cerebrospinal fluid is normal and the infection is confined to glands and blood stream the drug is efficacious. The earlier the treatment is started the better

is the result. The drug undoubtedly produces disappearance of the trypanosomes from the peripheral blood and in this way the transmission of infection to the flies is prevented and spread of the disease is checked. Chesternan (1932) obtained promising results in trypanosomiasis with combined treatment; two or three large doses of Bayer 205, *i.e.*, 3 doses of 1.5 gm. for adults at 3 or 4 day intervals were given, followed by tryparsamide. A rest is then given for two weeks; particular care should however be taken to prevent visual troubles. Manson-Bahr (1932) obtained similar results with the combined tryparsamide and Bayer 205 therapy of sleeping sickness, the results depending more on the age of the infection than on the size of the doses or length of treatment. Bayer 205 is given up to a total of 3 gm. in the first week and subsequently tryparsamide is pushed in tolerated doses keeping a watch on the optic symptoms.

Dosage and method of administration. In human beings it is advisable to start with 0.5 gm. intravenously and if it is well borne, to give 1.0 to 1.5 gm. after 24 to 48 hours. The dose can be increased up to 3 gm. but it is not advisable to give such large doses more than once a week. One gramme is usually given weekly, in most cases repeated two or three times. Larger doses should only be given when the drug is well borne. Kleine gave it in 1.0 gm. doses at each injection on the 1st, 3rd and 15th day. In children proportionately smaller doses, *viz.*, 0.4 to 0.6 gm. are given, and in them the drug may be given into the jugular vein. More than five injections are not advisable. Low and Manson-Bahr (1922) gave 1 gm. weekly in 10 per cent. solution till 10 gm. were given; sometimes they gave a 20 per cent. solution, the amount being as much as 12 gm. within 14 days. Others recommend the first 3 doses at shorter intervals—every other day. As a rule, a 5 gm. course is considered sufficient on the 1st, 3rd and 5th day; if trypanosomes reappear after the 4th or 5th injection it is better to change to another drug. The drug cannot be given intrathecally, as it is likely to produce alarming symptoms. According to some weekly intervals between injections allow the trypanosomes to become resistant.

The trypanosomes do not disappear from the blood so rapidly as under tartar emetic, atoxyl, etc. As a rule, the blood is not free from the parasites till the second or third day after the injection. Frequent examinations of thick blood films or centrifugalisation of blood in citrated saline are necessary in cases of relapses to demonstrate the presence of the parasites. Sometimes isolated parasites appear after a few weeks but these disappear without further treatment. The best test for cure is to inject the infected blood into small experimental animals and see if the disease can be transmitted. Clinically, the action of the drug is apparent by disappearance of the glandular swellings in the neck, diminution in the size of the spleen, improvement of the blood picture, increase of body weight and general mental well-being.

In encephalitis lethargica or 'sleeping sickness' it has been tried but found to be quite useless. It has also been tried in diseases caused by spirochaetes, *e.g.*, syphilis, yaws, etc., without success. Kala-azar and filariasis are said to be favourably influenced but it has no curative action on these conditions.

Toxic effects. The drug is not harmless and should be carefully handled. An erythematous rash sometimes appears, commencing on the forearms and spreading to the rest of the body. The eruption consists of central raised papules, rather patchy in distribution and finally it disappears by desquamation. Pruritus is a constant accompaniment, purulent conjunctivitis and stomatitis may occur. Albumin in the urine generally occurs after the second or third injection, and there may be blood and casts; anuria may occur. Symptoms of urinary irritation may subside after the termination of the course of treatment, but occasionally they persist. When patients are undergoing treatment a careful watch should be kept on the blood and the urine. The presence of albumin in the urine gives a warning although many authorities do not consider it a contra-indication to the use of the drug. Care, however, is indicated. Albuminuria may sometimes occur even after small doses. In many cases it disappears without leaving any permanent effects behind. Mayer, Kleine and others hold that albuminuria is

not necessarily an indication for the interruption of the treatment in patients whose kidneys are at other times normal. In some cases hæmolysis is produced. Optic troubles have not infrequently been observed. The Sleeping Sickness Commission in Portuguese West Africa in 1923 concluded, from their observations, that though Bayer 205 caused rapid disappearance of the trypanosomes, nephritis and in some cases amblyopia leading to complete amaurosis, militated against its general employment.

Prophylactic uses. Experiments conducted in Africa show that Bayer 205 and Fournau 309 have a definite prophylactic value. They afford protection for a long period, provided that the drugs are employed for the protection of healthy individuals. Healthy adults should be given two injections of 1.0 gm. each, younger people 0.5 gm., children 0.25 gm. and babies 0.1 gm. and each at an interval of 2 to 3 weeks. Sterilization of the blood of patients should also be carried out by treatment with atoxyl and other arsenicals. Recently, Lyndhurst Duke has shown that a single dose of 1 gm. of Bayer 205 given intravenously will protect a man for at least 113 days from infection by tsetse carrying cyclically *T. rhodesiense*. The administration of a second dose three weeks or so after the first enhances the protective effect of Bayer 205. Within certain limit the protective effect is directly proportional to the number of doses given, but the exact mode of action is not known. It is probable, though not definitely proved, that the protection conferred by Bayer 205 is greater against *T. rhodesiense* than against *T. gambiense*.

Mode of action. The mode of action of Bayer 205 is not properly understood. The drug produces no action on trypanosomes *in vitro*. After injection a trypanocidal substance can be demonstrated in the blood, milk, urine, etc., which may be the drug itself or a compound of it or some substance having no chemical relationship to it. A 1.0 per cent. solution of the drug lessens or abolishes the coagulation of blood serum by heat. Ehrlich considered the drug to be directly parasitocidal. Kleiger and Weitzmann (1926) injected cultures of trypanosomes together with Bayer 205 in experimental animals and found that they manifested an increased resistance which in some of them sufficed to ward off an attack. This increased power of resistance is not attributed to the protective power of the drug alone as the same phenomenon was observed in infected animals treated with Bayer 205. It is suggested that the

drug combines in some way with the trypanosome cell, producing a heterogenic antigen capable of stimulating the formation of specific antibodies. The action of the drug is not therefore purely parasitocidal; along with this property there may be an immunizing activity which completes the cure and affords an increased resistance in subsequent infection. Reiner and Koveskuty (1927) tried the drug in trypanosome infections of mice and concluded that Bayer 205 exerts its action directly on the parasites. But it did not alone kill the trypanosomes, hence the animals must have taken some part in the curative process.

Toxicity. Maximum tolerated dose in the mice is 0.01 gm. per 20 gm. body weight, in guinea-pigs 0.3 gm. per kilo. body weight; in rabbits 0.3 to 0.5 gm. per kilo. body weight.

Other Drugs in Trypanosomiasis

Arsenicals. Trypanosome infections were first treated with preparations of arsenic by Bruce (1895) and Lingard (1899) who employed them in animal trypanosomiasis. Later, Laveran and Mesnil (1902) used inorganic arsenic in an attempt to cure trypanosomiasis in laboratory animals.

Atoxyl (soamin). Atoxyl was employed by Koch (1907) in Africa in the treatment of sleeping sickness. The preliminary reports inspired great hopes, but later it was found that relapses frequently occurred, while optic atrophy was by no means uncommon. For details see the chapter on arsenic.

Tryparsamide. This drug was introduced for the treatment of trypanosomiasis by Drs. Brown and Pearce of the Rockefeller Institute. The preliminary experiments on laboratory animals were very encouraging, and further work in the Congo has strengthened the belief that in this drug, we possess a potent trypanocide. For further details, see the chapter on arsenic.

Fourneau 270 or sodium-4-acetyl amino-2-hydroxyphenyl-arsinate.

The action of this compound in sleeping sickness was first investigated by Ledentu and Daude (1926). Preliminary observations indicated that in the first stage the dose of 0.001 gm. per kilo. of body weight led to a disappearance of trypanosomes from the glands in 48 hours. Levaditi, Nicolan and Galloway (1926) have tested the prophylactic action of 270 when given by the mouth to rabbits subsequently infected with nagana. The drug has a prophylactic value but it is inferior to tryparsamide.

Fourneau 269 and 417. Two other compounds belonging to the above series were also used in trypanosomiasis. These can be given by the mouth, but the results have not been satisfactory.

Acetylarsan or oxy-acetylaminophenyl arsiniate of diethylamine. This drug has been used by Van den Branden (1922) in the treatment of chronic trypanosomiasis. The results were not as satisfactory as with tryparsamide. For further details, see the chapter on arsenic.

Antimonials in trypanosomiasis. Antimony was first introduced in the treatment of trypanosomiasis by Plimnier and Thompson (1908) who found that injections of potassium and sodium antimonyl tartrates cure infections of *T. brucei* or *T. evansi* in laboratory animals. It was formerly given intramuscularly but it caused great pain. It was then given intravenously. Excellent results have also been reported by the subcutaneous injection of antimony oxide suspended in equal parts of glycerine and water. This is practically painless.

Various organic preparations of antimony like antimonosan have been tried from time to time without much success.

Bismuth in trypanosomiasis. Colloidal bismuth and a basic oxyaminophenyl arsinat of bismuth have been tried but the results are not encouraging.

Quinoline derivatives. Derivatives of anil- and styryl-quinolines have been tried in trypanosomiasis. The results are successful in rabbit trypanosomiasis. Clinical results have not been satisfactory.

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SECTION III

REMEDIES USED AGAINST MALARIA

CHAPTER XVI

GENERAL CONSIDERATION

Malaria of all diseases is the greatest source of trouble to everyone living in tropical and subtropical climates. A résumé of its geographical distribution given by Rogers (1928) shows how widespread the disease is all over the world. During the Great War it caused the greatest loss of effective man-power, the largest invaliding and subsequent pension roll of any one disease. In India there are few malarial foci where it attains the same degree of virulence and intensity, as it does, for example, in Africa, Southern Italy and Greece, but the disease is so prevalent and widespread that India probably is one of the most malarious countries in the world. This is amply proved by statistics of the Public Health Commissioner with the Government of India. Malaria is still the principal cause of sickness among both the civil population and the army in India. A very large proportion of the troops, both British and Indian, suffer from it every year. Sir Andrew Balfour estimated the direct annual cost of sickness attributable to malaria in the British Empire to be roughly 52,000,000 to 62,000,000 pounds sterling and the annual world death-roll to be 2,000,000. The share of India might easily be half that amount. In India alone, according to James (1920) there are 1,300,000 deaths from endemic malaria in an ordinary year. Fortunately this is one of the few diseases against which true specific remedies are available. A thorough understanding of the action and uses of such remedies is therefore of vital importance to the medical profession in tropical and sub-tropical climates.

Incidence of malaria. The distribution of the three species of malaria parasites throughout the world has been studied in an exhaustive memoir by Knowles and Senior White (1930). This memoir includes

an analysis of all the available literature for the first thirty years of the present century and of a wealth of unpublished information with regard to India. Their main conclusions are:—The distribution of malaria in general throughout the world is limited in north and south hemispheres by the summer mean isotherms of 60°F.; the distribution of *P. falciparum* throughout the world is limited in both hemispheres by the mean summer isotherms of 70°F.; the distribution of *P. malariae* throughout the world shows a most curious and patchy distribution, suggesting that this is a dying species. The parasite findings both in peace and war differ as between military and civilian populations for reasons given. Mixed infections are relatively common, and constitute some 3.7 per cent. (or more) of the world. The relative gametocyte output for the three species is for *P. vivax* 21 per cent., *P. malariae* 45 per cent., *P. falciparum* 19 per cent., but, owing to the tremendously heavy production of merozoites by schizogony in the last named species, it is the one associated with epidemic malaria. In India (at least) the maximum output of gametocytes by *P. falciparum* appears to occur after the close of the transmission season, and this may be a very important factor in checking epidemics.

In England malaria existed in the low-lying countries. In France, Germany and Holland benign tertian infection exists, the carrier being *A. maculipennis*. In Macedonia both benign tertian (*P. vivax*) and malignant tertian (*P. falciparum*) forms exist and severe epidemics are known to occur. In Russia, Siberia, Albania and Palestine highly malarious areas are in existence. In India *A. culicifacies* and *A. stephensi* are the most important carriers. And in the Malay States *A. maculatus*, *A. funestus*, *A. aconitus* carry infections and *A. listoni* and *A. minimus* are associated with malignant tertian infections. Recently *A. ludlowi* has also been reported in India. *A. ludlowi* is the chief vector in the Dutch East Indies, Philippines, New Guinea, Africa, Algeria and Egypt. In South America (Brazil and Argentine) malaria is prevalent, the carriers being *A. tarsimaculatus* and *A. argyritarsis*.

Epidemiology. The main factors favouring high prevalence in the Punjab according to Gill (1923) are:—(1) The high relative humidity resulting from heavy rainfall in July and August; (2) A low spleen rate, indicating absence of temporary immunity due to recent attacks of malaria. (3) Economic distress and high price of food. (4) The occurrence in previous years of outbreaks of malaria. Such factors also play a part in other places. The necessity of a mean temperature of about 60°F. to enable malaria to be prevalent has been appreciated. This mean temperature must be maintained for sixteen days to allow full development of *P. vivax*, while in Macedonia a higher temperature is necessary for development of *P. falciparum*. Elevation and consequent low temperature limit the prevalence of the disease. In Kashmir at elevations of 6,000 to 8,000 feet, *A. maculipennis*, *A. fuliginosus* and *A. willmori*

are present in abundance, but no malaria exists because the temperature is not high enough for the parasites to develop.

Species and varieties of malarial parasites. Very few authorities now doubt the existence of three species, *i.e.*, *P. vivax* (benign tertian), *P. falciparum* (malignant tertian) and *P. malariae* (quartan). Recently, *P. ovale* has also been described. There is a tendency to further subdivide these recognised species into minor varieties. The plurality view has been greatly strengthened lately by thousands of inoculations carried out in the treatment of G. P. I. and other nervous diseases. Cultures of the parasites have furnished additional evidence. The question of further subdivisions of the three primary types is more difficult though a quotidian variety of the sub-tertian has been recognised by some. Stephens has described *P. tenue*. Marchoux (1925) suggested that each of the three recognised species of malarial parasites exhibits different races with varying geographical distribution and morphology. The protozoologists are generally against the parthenogenesis theory of Schaudinn, and Ross's view that relapses are brought about by the spores of the asexual schizonts, which during latency are too small in number to be detected by the most careful microscopical examinations of the blood, furnishes a simple and likely explanation. Sinton has shown that parasites may be present in less than 1 c.mm. of blood, and yet may not be detected except by cultural method. The view that plasmodia are attached to the surface of the red blood corpuscle and not within it is supported by a number of workers. The ratio of crescents present is usually one male to two or more females.

Duration of infection in mosquitoes. The question as to how long anophelines once infected with malaria can remain infective to man has also been worked out by inoculation experiments. Infection could be produced by bites of *A. punctipennis* up to 55 days after feeding on crescents, and sporozoites were found in it.

Methods for studying the action of anti-malarial remedies. It will not be out of place to mention here the method by which the efficacy of the various antimalarial remedies is tested. Many observations recorded in the subsequent sections have been drawn as a result of these experiments.

1. Tests on the parasites of avian malaria—Type 'Proteosoma'.

These tests were primarily discovered by Copanaris, the brothers Sergeant, Giemsa and Marks, and were established as a routine laboratory practice by Roehl, who adopted the procedure of administering drugs to birds through an oesophageal tube passed into the stomach. The test consists in inoculating intraperitoneally a small quantity of blood from the bird which is being tested, into another bird of the same species. If the inoculated bird does not show parasites within a month, a second bird is inoculated in the same way. Canaries which have

passed the isodiagnostic test are infected with a known species of bird malaria (usually *Plasmodium relictum*, Grassi and Feletti) by direct blood inoculation, intramuscularly or intraperitoneally. The blood used for infecting the birds is taken when the parasites have reached their maximum number. It may be injected whole or diluted with physiological or citrate saline solution (one drop of blood in two drops of citrate solution). Four hours after infection, treatment with the drug to be tested is begun, and is continued daily for six days. The drug is administered through an oesophageal tube into the stomach, the usual dose being 1 c.cm. of a solution of known strength per 20 grammes body weight of the bird.

After ascertaining the maximum strength of the solution which the bird is able to tolerate in the dose given, a series of experiments is made to ascertain whether this strength of the drug causes delay in the appearance of parasites in the peripheral blood, and, if so, what further dilutions also cause a distinct delaying effect. The period of delay is ascertained by examining thin blood-films every day, the first day on which parasites can be found being compared with the first day on which they can be found in untreated control birds. In the control birds the parasites generally appear on the fifth day after infection. A drug is not considered to have a distinct therapeutic effect unless the delay in the appearance of parasites in the blood of treated birds is at least to the tenth day.

The birds used, should, whenever possible, be obtained from a country where natural infection with avian malaria parasites does not occur. When it cannot be guaranteed that the birds are free from previous infection, each bird should be examined prior to its inclusion in the series. It may be necessary to inoculate a specimen of blood into another bird to prove freedom from infection.

The test is used chiefly for the purpose of making a preliminary selection of those drugs which give an indication that they may be worthy of further study, from the numerous preparations which are submitted for examination.

2. Tests on the parasites of avian malaria—Type 'Halteridium.'

As long ago as 1906 the brothers Sargent showed that quinine has no curative action against parasites of the type 'halteridium' (*Hæmoproteus columbæ*), which occur naturally in pigeons and other birds. Since 1908 it has been the practice to try the effect of other drugs on these parasites as well as on those of the type 'proteosoma.' The species of parasite commonly used is *Hæmoproteus orizivora* which occurs as a natural infection in rice finches from Java and some other Eastern countries. It is a parasite of which only the gametocytes (male and female) can be found in the peripheral blood, the vegetative non-sexual cycle being passed in the endothelial cells of the lungs, the liver and other internal organs. Thus the object of therapeutic

tests with this parasite is chiefly to ascertain whether the drug to be tested has a gametocidal action. For this purpose one selects two or three naturally infected finches, and after having made a daily count of the parasites during a short period (four or five days), one treats the bird with the drug in the same way as in trials on 'proteosoma' parasites of canaries. The effect of the drug is observed by noting whether the parasites disappear or are greatly diminished in numbers as a result of the treatment.

3. *Tests on the malarial parasites of monkeys.*

It has recently been found that several varieties of malarial parasites which occur naturally in monkeys in the Far East and in Africa can be utilised for experimentally controlled therapeutic tests of antimalarial remedies. In particular, it has been found that a species of malaria parasite occurring naturally in monkeys of the species *Silenus irus*, when transferred by blood inoculation to *Silenus rhesus* or *sinicus* causes an acute infection which, when untreated, invariably ends fatally, but when treated with quinine, is cured or can be maintained at a low parasite level for months. In India, in the Malay States and in England, a beginning has been made in the application of this finding, to the practical purposes of therapeutic tests, and already results of a few carefully controlled trials with atebrin in comparison with quinine have been reported. The ability to work on the subject with monkeys as well as with birds is a noteworthy addition to the means at our disposal for evaluating the relative efficacy of antimalarial remedies.

4. *Therapeutic tests on human malaria induced intentionally.*

Since the introduction of malaritherapy, it has become possible to study the therapeutics of the disease under controlled conditions and to devise some useful tests for ascertaining the efficacy of preparations for prophylactic and curative purposes. It is to be understood, of course, that in all therapeutic tests on induced malaria, every endeavour should be made to imitate natural conditions as closely as possible. An essential condition is that the patients must be infected in the natural way by the bites of infected mosquitoes and not by the direct inoculation of malarial blood.

5. *Tests on human malaria contracted in the field.*

In general, the only test which can be conducted on patients who contract their infection in the field is a test of the immediate therapeutic value of a short course of the drug to be tested in comparison with the immediate therapeutic value of the same course with quinine.

6. *Microscopical study of the parasites in cases treated with a specific remedy.*

Diagnosis should be made by blood examination, thick films being preferred; as the parasites are more readily found by this means.

A thin film should also be examined to determine the species of the parasite. Injection of provocatives to bring the parasites into the peripheral blood stream has been advocated. Differential leucocyte counts have proved to be of very little value; a complement fixation test has been worked out but it is not satisfactory. The culture method is certain. Given a competent observer, examination of 100 fields of a thin film plus a reasonably careful examination of a thick film will enable a positive diagnosis to be made in 95 per cent. of all cases of developed malaria; but will only discover 67 per cent. of the cases of mixed infection. Whereas benign tertian infections tend to chronicity and relapses, and quartan infections to even greater chronicity with but few febrile manifestations, a preliminary study of untreated cases of malignant tertian malaria shows that infection usually does not persist in the individual in the absence of repeated fresh mosquito-borne infections.

Splenic index. The spleen rate is a simple and rapid method of estimating the degree of malaria in an affected area and gives results closely parallel to the more laboriously ascertained parasite index.

STUDY OF CURES

I. Natural cures. The life of a parasite depends on the life of the host, if the host dies millions of parasites which are living in it die also. There is a tendency in chronic protozoal infections for a condition of balanced equilibrium to be reached between the patient's power of resistance and the parasitic invasion. This condition one may term 'immunity' or better 'tolerance.' Hence their rate of multiplication is decreased by the formation of non-multiplying forms (gametocytes) from merozoites or asexual cycle. In untreated cases of malignant tertian infection, the fever subsides as soon as gametocytes alone are present in the blood. Thus a patient suffering from malaria is, after a fairly long period, cured of the disease without any treatment, provided, of course, he does not get reinfection during this time. Patients who leave the tropics are generally completely cured in about two years, though here and there one comes across with cases which persist for five years or more. Natural cures are partially brought about by excessive gametocyte formation which, so to say, converts the asexual cycle to non-multiplying gametocytes. Another factor also comes into play, especially when the patient has resided in a non-malarious district for a long time, and that

is senility of the gametocytes and their death from senile decay. It has been demonstrated that when the asexual cycle of *P. falciparum* is destroyed, for example, by quinine, gametocytes still occur in the peripheral blood; the sexual forms are gradually destroyed, though no further treatment is given (gametocytes can only multiply in the stomach of the mosquito).

II. **Artificial cures.** These are produced by the administration of certain antimalarial remedies, which act by destroying the asexual parasites, but have less effect on the gametocytes. The important factors concerned in these artificial cures are:-

(1) *The rate of parasite multiplication.*—It is known that the subtertian parasite multiplies at the rate of 24-32 merozoites in 48 hours, and according to Acton, is most influenced by quinine, while the benign tertian parasite forms 16 to 24 merozoites in 48 hours and is not so easily destroyed by quinine. A single *P. vivax* produces 24 new parasites in 48 hours, and at this rate of multiplication it can produce 250,000,000 descendants in fourteen days, a number which would produce about fifty parasites per c.mm. of blood. This is a number which can be detected microscopically but which will not give rise to fever. The next generation however will produce sufficient parasites to cause fever. A remedy which kills 96 per cent. of the parasites of the benign tertian form in 48 hours will not cure the disease, for it will only prevent the multiplication of parasites and will not reduce their number. As a matter of fact the rate of multiplication of parasites is somewhat less than that indicated above, because as soon as the multiplication of the parasites is checked, sexual forms appear, and since those can only reproduce in the body of the mosquitoes, they are inactive as far as the human body is concerned. That the difference in the rate of multiplication is not the only factor concerned is evident from the fact that the quartan parasite has the slowest rate of multiplication, i.e., 6 to 12 merozoites in 72 hours yet it is the most refractory to quinine.

(2) *Rate of parasite destruction.*—The percentage of each brood of parasites destroyed by continuous administration of antimalarial drugs is the other important factor. According to Ross, a man of average weight

(10 stones) has about 3,000,000 cubic millimetres of blood and allowing for 5,000,000 red blood corpuscles in each c.mm., there will be 15,000,000,000,000 red blood corpuscles present in the body. If there is one parasite per c.mm. of blood, it means 3,000,000 in the body. The lowest number of asexual parasites causing fever has been calculated to be about 100 per c.mm., *i.e.*, 300,000,000 parasites in the total quantity of blood. In severe infections of malignant tertian type the number of parasites is considerably higher, as many as 12 per cent. or more of the red blood corpuscles being infected. When the number of parasites falls below 300,000,000 they produce little or no symptoms—'parasitic relapse'. Theoretically a single parasite would in three weeks' time multiply sufficiently to produce fever, and therefore, to effect a cure every parasite must be destroyed. It is also known that in latent malaria, a large number of parasites can exist and multiply in the body without producing any apparent symptoms and any condition which lowers the vitality of the host, *e.g.*, unfavourable climate, fatigue, etc., tends to convert the latent into an active disease.

As regards the rate of destruction, it is known that a single dose of any of these drugs is not sufficient to effect a cure, but a series of doses has to be given. It has been shown that a large dose of quinine is cast out of the body rapidly, the tissues in this way protect themselves against the foreign chemical introduced into the body. The parasites in the host are not like fishes in a bowl which can be destroyed by mixing a single dose of poison with water. Many of them make good their escape and the drugs have therefore to be given in repeated doses daily, and continued for some time to keep down the parasites and produce a cure. These facts lead us to conclude that the rate of destruction must be below 100 per cent. The rate of destruction of the parasites, in order to produce a cure, has been calculated mathematically and found to be over 98 per cent. of each generation. It is well known that quinine causes a rapid amelioration of symptoms in all types of fever, and parasites also disappear from the peripheral blood. This effect is probably due to reduction of parasites from over 300,000,000 (febrile stage) to below that number (afebrile stage). Ross found

that 8 grains of quinine daily sufficed almost invariably to improve symptoms greatly while it was being taken, but it failed to produce complete cure even after 6 weeks' administration. Acton found the cure rate in benign tertian infection to be 20 per cent. after one month's treatment with quinine.

1. **Phases of artificial cure.** In the production of artificial cures, *i.e.*, those produced by drugs, several facts have to be taken into consideration.

- (A) The immediate and relative effect of the remedy used.
- (B) Partial cures or relapses.
- (C) Complete cures or sterilisation.

(A) **The immediate effects.** The parasitocidal effect is studied by noting the rapidity with which the asexual forms disappear from the peripheral blood and symptoms are relieved. Too much importance cannot however be attached to the picture presented by the peripheral blood as this gives little indication of what is brewing in the deep-seated foci. The curative effect, according to Acton, varies with the alkaloids used and species of parasite present. In malignant tertian infection schizonts become adhesive and form clumps and so block the smaller vessels of the brain and intestines, giving rise to pernicious symptoms. When quinine is given the trophozoites disappear within 24 hours after the first dose; gametocytes are not affected at all, as they have been found to exist for as long as 40 days after commencing treatment, and they are still able to undergo sexual reproduction in the stomach of anophelines. It has been demonstrated that if the asexual cycle is destroyed and the patient is put on ordinary tonic treatment (with no quinine whatever) gametocytes that are present either die of senility within a few weeks or are destroyed by the cells of the body, the patient undergoing a complete cure.

In benign tertian infections the asexual cycle takes place in the peripheral circulation and when quinine is given the young trophozoites disappear, within 24 hours after the first dose. The older trophozoites and the developing schizonts are not so easily affected, as they can be seen up to 48 hours (because sporulation is not completely prevented, and a slight attack of fever is often observed on the third day). The gametocytes disappear from the blood in 4 to 5 days, showing that they are less resistant to quinine than malignant tertian gametocytes.

The method of administration is an important factor in the rapidity of cure; the intravenous method is believed to be the most rapid in action and next come the intramuscular and the oral routes. As regards the different alkaloids of cinchona bark, the amorphous alkaloids which go by the name of quinoidine, have little effect, while the crystallisable alkaloids are all effective. If during the course of treatment parasites

reappear, it is certain that either the patient is avoiding treatment, or the interval between doses is too long or the alkaloid is not being absorbed.

(B) *Partial cures and relapses.* The destruction of the asexual cycle by the cinchona alkaloids is a gradual process of fractional destruction and it is obvious that one single dose or a few doses given at short periods do not suffice to effect a cure. As it is impossible to find out the exact time of liberation of each young brood, the ideal plan will be to give a continuous treatment long enough to affect many generations of the parasites (5 to 6 weeks to destroy 10 to 15 generations). Relapses in benign tertian infections cannot be attributed to insufficiency of quinine treatment, as in some of Acton's experiments this was carried on from 3 to 5½ months and in spite of this 50 per cent. relapsed. After the War there was a great outcry against the use of quinine in malaria because it failed to cure many cases. These observations were inconclusive and there were many sources of error. Quinine, if properly administered, will rapidly relieve the symptoms due to malarial parasites and if properly followed up, will prevent the parasite from causing death or serious damage to the patient. In spite of all the precautions, however, a permanent cure may not be obtained and relapses may occur. What then is the explanation of these relapses? The following possible explanations have been suggested regarding the escape of the parasites from destruction:—

(1) *Production of quinine-resistant forms.* Against this view is the fact that if quinine is properly administered in adequate doses, it causes immediate disappearance of the asexual parasites from the blood. It has often been stated that the first attack is more easily cured than subsequent ones and this has been proved by James' experiments with induced malaria. MacGilchrist (1915) in 149 cases in the Presidency goal found no cases of 'quinine-fastness' or even 'relative fastness' on the analogy with atoxyl in trypanosomiasis. The brothers Sargent (1921) carefully investigated the subject in the treatment of canaries infected with *Plasmodium relictum* and have proved this resistance to be of very rare occurrence. Acton and his colleagues in Dagshaki put a large batch of men on quinine treatment, and as they relapsed, repeated the treatment by giving a complete course of quinine again. They found that the cure percentage remained constant, i.e., 20 per cent. from the first to the fifth course of treatment. It is obvious that if the resistance of either the parasites or the host had altered, they would certainly have not become quinine resistant; they disappeared from the peripheral blood after quinine administration, in as short a time with the fifth relapse as with the first. Investigations by Fletcher (1923) showed that the alleged resistance to quinine in many of the cases during the Great War was apparent and not real, and that often it was due to quinine not being swallowed. The drug also may be adulterated. In any case if quinine resistant cases occur they are so few that if scrupulous care is taken

in the details of the treatment they may be ignored altogether. Quinine fastness or resistance of a particular strain of parasite cannot therefore be accepted as a cause of relapse. What, then, is the cause of relapses after quinine treatment? The parasites may take up their abode in the capillaries of the internal organs or in areas where body fluids do not freely reach them, or the patient's powers of resisting the infection (immunity) may not be stimulated.

The existence of back-waters, such as the spleen and the bone marrow, where owing to adsorption of the alkaloids by the tissues, quinine does not penetrate and parasites can go on multiplying, has been held as one of the causes. Recent studies have shown that it is in the finest capillaries of the grey matter of the brain and in the reticulated sinuses of the spleen and bone marrow that segmentation takes place and asexual parasites chiefly congregate. Some evidence has also been produced to show that in the blood-vascular system there are regions which are kept almost free from quinine throughout the period of quinine treatment. But it has been pointed out that in malignant tertian infections, schizogony occurs in the deep-seated areas, but in spite of this quinine is quite effective and acts as a specific, while in benign tertian where schizogony occurs in the peripheral blood it gives a lower cure rate.

(2) *Failure of quinine due to new species of parasites.* The opinion of protozoologists is against this view. The profound difference in the virulence between ordinary endemic malaria and malaria in epidemic form was thought to be due to different varieties of parasites, but Wenyon (1921) who examined countless blood films showed that the parasites were the same in both cases.

(3) *Failure due to non-absorption of quinine.* Failure due to non-absorption of quinine owing to catarrhal conditions and inflammation of the gastro-intestinal tract has been assigned as one of the causes. Observations show that quinine, as a rule, is readily absorbed from the gut even under such conditions. This can be demonstrated by testing the urine with Meyer's reagent.

It will be seen from the above that no satisfactory explanation is forthcoming and all that can be said is that relapses are due to incomplete destruction of the asexual cycle by the cinchona alkaloids. If all preliminary infections were really cured the incidence of malaria would diminish. Statistics of the Indian Army show that only 23.5 per cent. of the cases coming under treatment in endemic malarial areas are primary infections, while 76.5 per cent. are relapses and reinfections. If reinfections are prevented and quinine treatment is thorough, the percentage of relapses is diminished.

It has also been pointed out that relapses are much more common in cases of benign tertian than in malignant tertian. The question of individual resistance of the patient is important, as some persons acquire

malaria much more readily than others, and this factor also plays an important part in the quinine treatment of malaria. Proper treatment with cinchona alkaloids appears to be a very potent preventive measure. In relapsing cases, all predisposing causes, *e.g.*, excesses of any kind, fatigue, exposure to heat and cold, should be avoided. Transfer to a non-malarial area such as a hill station is advised for persistent cases.

(C) **Complete cure or sterilisation.** This can be brought about in three possible ways:—

(1) *Response of the defensive mechanism of the body.* The effects of the alkaloids on the tissue cells of the host, making the erythrocytes noxious, causing the phagocytes to destroy the parasites or by the formation of antibodies.

(2) *Selective action of the alkaloids on merozoites in the blood.* It has however been found that large doses of quinine given during the cold stage have no greater beneficial action than when given at any other time. It has also been shown that high concentrations of quinine in plasma, though they give rise to symptoms of cinchonism, do not produce a cure more easily.

(3) *Selective parasitocidal action of different alkaloids.* Acton (1922) showed that although all crystallisable alkaloids affect both tertian and subtertian forms of parasites, quinine and cinchonidine (laevo-rotatory) appear to have a specially marked action on the malignant tertian parasites while cinchonine and quinidine (dextro-rotatory) have more powerful action on the benign tertian forms. He suggested that the efficacy of quinine against malignant tertian parasites is due to the fact that they sporulate in the mesenteric vessels, where quinine is present in greatest concentration, while the benign tertian and the quartan parasites are found in the peripheral blood stream where the concentration of quinine is much lower. Some other workers have produced evidence to show that quinine is more potent against the schizonts of *P. falciparum* than against those of *P. vivax*, whereas for the gametocytes the condition is reversed. The reaction of quartan malaria to quinine is again different and in this form it gives the most unsatisfactory results, whereas, quinidine is thought to be more effective in these cases. The Medical Research Council Report No. 96 (1925) does not bear out a preferential action of quinidine on benign tertian or of quinine on the sub-tertian infection.

CHAPTER XVII

THE CINCHONA ALKALOIDS

The Cinchona alkaloids occur in the various species of two rubiaceous genera, *Cinchona* and *Remijia*, which are indigenous to the eastern slopes of the Andes in South America between the latitudes 10°N and 20°S. *Cinchona* comprises about forty species of evergreen shrubs or trees, which grow isolated or in small clumps in dense forests. The average height at which they flourish is an altitude of 3,000 feet to 10,000 feet above the sea level. Some of the species are found as high as 11,000 while others as low as 2,500 feet. The trees may reach the height of 80 feet and are valued for their bark, which contains certain potent alkaloids.

All the evidence goes to show that although the natives of those parts suffered from tertian ague, they did not know the febrifuge properties of the bark. They believed it to be heating and therefore unfit for use in fever. Markham who visited America to obtain seeds in 1880 testifies to the fact that the wallets of the native doctors never contained cinchona bark. It is probable that the Jesuit missionaries were the first to discover the virtues of cinchona bark. In 1630 Don Juan Lopez de Cannizares, Spanish Corregidor of Loxa, was cured of an intermittent fever by the use of this bark. In 1638 the Countess of Cinchon, whose husband was viceroy of Peru, was stricken with intermittent fever which refused to yield to any of the known remedies. The Corregidor of Loxa sent the viceroy some bark with the assurance that it would cure the Countess. She tried it with happy results and the bark was also tested on many patients. In 1640, on her return to Madrid, the Countess brought a quantity of the bark with her. It was used in England by Robert Talbor, a physician, in 1655 as a secret remedy. With this he cured the Dauphin of France and Louis XIV who purchased the secret for 2000 louis d'or and at the same time granted him a life pension of 2000 francs. When Talbor died in 1681, Louis ordered the publication of his method of curing tertian and quartan ague.

The reputation of the bark as a cure for ague was not maintained for long as a good deal of the bark imported was not cinchona bark at all. Many physicians found the remedy useless and controversies arose as to its value. In spite of these failures the isolation of quinine by Pelletier in 1820 created a fresh demand for it. The use of the bark

had become so extensive that fears were entertained that the supply from South America would be exhausted. Attempts were then made to transplant some of the species to other countries, and in 1852 the Netherlands Government determined to attempt the transfer of cinchona from South America to Java in order to cultivate it in regular plantations. For this purpose the botanist, Justus Charles Hasskarl, went to South America and remained there till 1854. He succeeded in collecting live plants and the seeds of several varieties, and from these the plantations were started. The British expedition was sent to South America under the leadership of Sir Clements R. Markham and plantations were started in India (in the Nilgiris and the Palnai Hills of Travancore) in 1860 and in Ceylon (Hakgala) in 1861. As early as 1866 there were more than one and half million of cinchona plants in the Nilgiri Hills, the species growing best being *C. officinalis*. Plantations were also established in the Himalayas, British Sikkim near Darjeeling and in the Karen Hills in Burma. The species growing best there were *C. succirubra* and *C. calisaya*.

Of the large number of species and sub-species only a few yields commercially valuable barks. They are :—

- | | | |
|--|--|------------------------------|
| I. <i>C. officinalis</i> var. | $\left. \begin{array}{l} \textit{condaminea} \\ \textit{bonplandiana} \\ \textit{crispa} \end{array} \right\}$ | yielding crown barks. |
| II. <i>C. succirubra</i> (Pavon), yielding red bark. | | |
| <i>C. pitayensis</i> , etc. | | |
| III. <i>C. lancifolia</i> | $\left. \begin{array}{l} \\ \\ \end{array} \right\}$ | yielding Columbian red bark. |
| <i>C. cordifolia</i> | | |
| IV. <i>C. nitida</i> | | |
| <i>C. mircantha</i> | $\left. \begin{array}{l} \\ \\ \end{array} \right\}$ | yielding grey bark. |
| <i>C. peruviana</i> | | |
| V. <i>C. calisaya</i> yielding yellow bark. | | |

The successful transplantation of cinchona was followed by a period of researches and experiment to find the proper ways and means of propagating the new plants. In Java all the varieties were found to possess a low percentage of quinine with the sole exception of *C. officinalis*; this variety however did not grow very well. In 1865, a new variety of *Calisaya* seeds were received from Bolivia by a merchant named Charles Ledger. Ledger who was an Englishman sent his brother to London to sell the seeds to the British Government, but as negotiations were not successful and as he feared that the seeds would lose their germinating power, he sold them to the Netherlands Government. These seeds were planted in Java in 1865 and the first analysis of the bark in 1872 showed that of all the *Calisaya* varieties this specimen gave the highest yield of quinine, the average quinine content being 6 per cent., exceptional samples yielding from 10—12 per cent. The plantation of this variety was therefore taken up, and large plantations were started by the Government as well as by enterprising private individuals. Cinchona cultivation flourished in Java and at present about

9 to 10 million pounds of quinine are produced annually on an average, this may be estimated from the fact that about 90 per cent. of the quinine supply of the world comes from that island. The maximum content of the alkaloid occurs in trees between the ages of seven and eleven years. *C. succirubra* has proved the hardiest and most easily cultivated species, and it gives a high yield of total alkaloids (10 per cent.), in which quinidine and cinchonine content preponderates over that of quinine. In the hybrids, *C. officinalis* and *C. robusta* the total alkaloidal content is very large, and of late years the quinine yield has also considerably increased.

Cupress cortex contains both cupreine and quinine and is obtained from *Remijna pedunculata* and other species.

The therapeutic effects of cinchona bark are due to the alkaloids present; of these quinine is the best known, while quinidine, cinchonine and cinchonidine have been used to a comparatively less extent in medicine. The alkaloids are contained in the cellular tissue of the phloem. In the leaves they are only present in small quantities but larger quantities are found in the stem bark increasing from above downwards as the root is approached. The alkaloids exist in the bark in combination with cinchotannic acid and quinic acid. The former is oxidised by exposure to a red colouring matter which is present in large quantities in *C. succirubra*. The principal dried barks used for the production of quinine are :—*C. succirubra* (red cinchona bark), 1,000 gm of good bark yielding at least 50 gm. of total alkaloids containing 15 gm. of quinine sulphate; *C. calisaya* (yellow cinchona bark) which with the same amount of bark yields 60 gm. of total alkaloid containing 30 gm. of quinine sulphate; *C. officinalis* (crown or Loxa bark) containing 5 per cent. of total alkaloids, of which 3½ per cent. is quinine; the bark of *C. lancifolia* or Columbian bark contains about 2 per cent. of the alkaloids with only a small proportion of quinine.

The bark is usually collected by felling the trees or by 'capicing'. These methods are now largely employed in preference to other methods and the plantations are so arranged that every year a large area is matured and the trees are ready for cutting down. The trees yield the maximum amount of alkaloids when they are 6 to 9 years old and it is about this time that they are cut down.

The total production of quinine is about 600,000 kg. per annum manufactured in 14 different factories; it is doubtful if this amount is sufficient for the needs of the whole world. It is said that even the present production is in excess of the commercial demand, but it is also true that owing to its high price, millions of people suffering from malaria cannot get it.

Composition of Cinchona bark. Pelletier and Dumas in 1820 isolated quinine from the bark and Cunningham predicted

long ago that probably the bark contained other alkaloids as well. Further investigations have shown that as many as twenty alkaloids and probably more, the majority of which have been isolated by Hesse are present in the bark from various species. These are divided into crystallisable and amorphous. The bark in addition to these alkaloids contains certain acids, neutral principles, colouring matter and traces of a volatile oil, gum, starch and other vegetable matter. The ash 1 to 2 per cent. consists mainly of calcium and potassium carbonates and a little silica. The large amount of ash present in cinchona febrifuge is due to the fact that magnesium sulphate is added to the alkaloidal mass in order to make it more amorphous.

Extraction of Cinchona alkaloids. The bark is dried and ground to a fine powder mixed with slaked lime, which is passed through a sieve of 40 meshes to the linear inch, sufficient water being added to make it damp. The addition of lime makes the subsequent extraction of the alkaloids easier. The mixture is made into a thin paste with water and put into vats. Caustic soda and warm paraffin oil are then added and the vats heated to 170°F. with frequent stirring of their contents; these are then allowed to settle when two layers form, the oil on the top containing the alkaloids and the exhausted bark below. The oil is decanted off and mixed with dilute sulphuric acid which dissolves all the alkaloids. The mixture on standing separates into two layers, the acid liquor containing all the alkaloids in solution. The alkaloids are then precipitated by adding caustic soda. The crude total alkaloids thus obtained, sometimes called cinchona febrifuge are further purified.

Cinchona Febrifuge. The cinchona febrifuge was first prepared in India in 1874 at the instance of Dr. J. R. de Vrij, who suggested the manufacture of a powder containing all cinchona alkaloids derived from *C. succirubra*. It was prepared by exhausting the powdered red bark with water acidulated with hydrochloric acid, precipitating the liquor with soda and drying the crude product. This continued to be the only product of the Indian factories until 1887 when quinine manufacture was started. In the meantime quinine began to be considered the only effective alkaloid in the treatment of malaria and there was a demand for barks containing a higher percentage of this alkaloid. The result was that cultivation of yellow bark from *C. calisaya*, *C. ledgeriana* and their hybrids, which contain higher proportions of quinine, was encouraged. About 1903 the scarcity of *C. succirubra* bark in India led to an alteration in the process of manufacture of cinchona febrifuge. This now consists of alkaloids which remain after the extraction of the quinine from the yellow bark, some quinine being

added to make it more or less similar in composition to the original cinchona febrifuge.

As met with generally, cinchona febrifuge appears to consist of any mixture of the bark extracts and by-products of quinine manufacture which makers wish to get rid of. Some of these mixtures are of excellent quality and contain a large percentage of the alkaloids, and are considered by many experienced physicians to be therapeutically as good as quinine; others are decidedly inferior and contain small proportions of the alkaloids. The following tables give the composition and the variations in the alkaloidal contents of different specimens which have been analysed.

ANALYSIS OF CINCHONA FEBRIFUGE

No.	Source of Samples.	Quinine per cent.	Cinchonidine per cent.	Quinidine per cent.	Cinchonine per cent.	Total crystalline alkaloid	Quinoidine (amorphous alkaloid) per cent.
1.	Dr. Vrij's analysis of Java febrifuge (1876)	2.9 to 22.2	24.0 to 60.4	2.8 to 5.4	18.0 to 54.0	..	0.4 to 21.0
2.	Cinchona febrifuge (total alkaloid of <i>C. succirubra</i>) ...	15.5	29.0	..	33.5	78.0	17.0
3.	Cinchona febrifuge from Mungpoo (Mac-Gilchrist 1914-15) ..	7.4	5.8	22.8	18.6	54.6	29.1
4.	Cinchona febrifuge Govt. of India (Gage 1922)	10.5	7.0	16.0	28.0	56.5	38.0
5.	Cinchona febrifuge tablet, Govt. of India (Howard 1918) ..	2.7	8.4	12.5	12.8	80.9	54.9
6.	Do.	8.0	21.0	4.5	21.0	54.5	80.0
7.	Cinchona febrifuge (Java) ...	5.8	12.2	8.7	20.0	46.7	41.8
8.	Do.	11.9	9.2	4.8	15.8	41.2	45.4
9.	Cinchona febrifuge (Quinetum), Europe.	8.5	7.0	8.6	28.8	52.4	44.7
10.	Cinchona febrifuge (Quinetum), used in League of Nations' clinical trial.	15.0	35.0	5.0	25.0	80.0	20.0

			CINCHONA FEBRIFUGE		Residual Alkaloids Indian
			Indian percentage	Javan percentage	
Quinine	7'40	11'5	3'0
Cinchonine	18'58	26'8	35'0
Quinidine	22'83	5'0	20'0
Cinchonidine	5'84	20'0	2'0
Total		..	54'65	62'8	60'0
Quinoidine	29'12	37'2	30'0
Water and ash	16'23	...	10'0

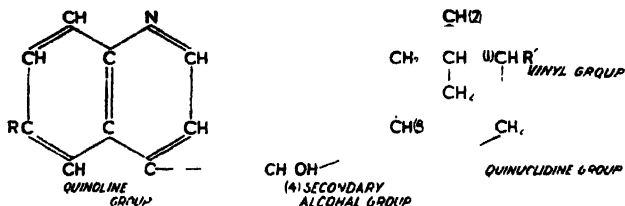
A perusal of the above results will show that the amount of the crystalline alkaloids having an antimalarial action present in the two brands of 'cinchona febrifuge,' as well as in the residual alkaloids, is sufficient to produce therapeutic effects. It will be seen also that 'cinchona febrifuge' has no fixed composition and is frequently adulterated. The 'cinchona febrifuge,' as issued from the Government factories in India, is mostly the residual alkaloid preparation from the bark of *C. ledgeriana* after most of the quinine has been removed.

Quinetum and Quininum. Another product of cinchona bark, similar to cinchona febrifuge, used in India is quinatum. According to some, it is a substance like cinchona febrifuge containing all the alkaloids, but only 15 per cent. of quinine and 5 per cent. of quinidine. According to others, it is a mixture of cinchona alkaloids as they occur in the bark of *C. succirubra* and consisting of sulphates of cinchonidine, cinchonine and quinidine with smaller quantities of the sulphates of quinine and amorphous bases. Some even say it is simply a mixture of amorphous bases of cinchona bark, the crystalline alkaloids having been previously removed. The confusion with regard to 'quinatum' has recently been disentangled by the Commission of Expert Malarialogists appointed by the League of Nations. The name 'quinatum' should be reserved for a preparation consisting of quinine, cinchonidine and cinchonine in equal parts. If this preparation is made by extracting those alkaloids from the bark of *Cinchona succirubra* (which usually contains them in approximately equal quantities), only a small addition of one or other of the crystalline alkaloids will be necessary in order to equalise the amount of each alkaloid in the preparation.

Quininum is an extract prepared according to a French formula. It contains all the constituents of the bark except the woody fibres.

Chemistry of Cinchona alkaloids. The following description of the chemistry of cinchona alkaloids is taken from Findlay's 'Recent Advances in Chemo-therapy' (1932).

Alkaloids of Cinchona. The four chief crystallisable alkaloids derived from cinchona bark are quinine, quinidine, cinchonine and cinchonidine, but in addition to these, over twenty other alkaloids have been isolated from various species of cinchona and cuprea. The majority of these alkaloids, the non-crystallisable and amorphous alkaloids, are sometimes described collectively as quinoidine. The four alkaloids, quinine, quinidine, cinchonine and cinchonidine, form two pairs of isomerides of which each member of the first pair differs from each member of the second by the residue of a methoxyl group— CH_3O . In addition, the members of each pair yield for the most part the same products under the action of various reagents, and the products furnished by the two pairs form parallel series differing constantly by the residue of a methoxyl group— CH_3O . Rahe has assigned the following general formula to this group of alkaloids.



In quinine and quinidine, $\text{R} = \text{OCH}_3$ $\text{R}' = \text{CH} : \text{CH}_2$

In cinchonine and cinchonidine $\text{R} = \text{H}$. $\text{R}' = \text{CH} : \text{CH}_2$.

In cupreine, $\text{R} = \text{OH}$. $\text{R}' = \text{CH} : \text{CH}_2$.

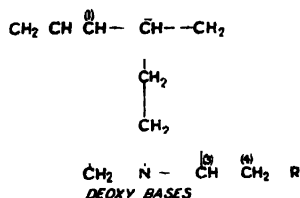
In the hydro-bases, R' becomes $\text{CH}_2 : \text{CH}_3$.

In the alkyl cupreines R becomes OAlk (homologues of quinine).

In the alkylhydrocupreines and alkylhydrocupreidines, R becomes OAlk , and R' becomes $\text{CH}_2 : \text{CH}_3$. (homologues of dihydroquinine and dihydroquinidine).

The carbon atoms numbered (1), (2), (3) and (4) in the general formula are asymmetric. Since cinchonine and quinone in which the asymmetry of the carbon atom (4) has been destroyed by the conversion of the secondary alcohol group (CHOH) into a carboxyl group (CO), are both dextrorotatory and both yield β -vinyl-4-quinuclidineoxime of the same optical activity, it follows that cinchonine, cinchonidine, quinine and quinidine must be optically identical as regards carbon atoms (1)

and (2), that the distribution in space is the same about these atoms, and in all four cases is dextro-rotatory in total effect.



The deoxy-bases, obtained from cinchonine and quinidine and from cinchonidine and quinine are structurally identical, but differ in optical properties, the first pair being dextro- and the second pair laevo-rotatory. These deoxy-bases have the same general formula where R is $\text{C}_9\text{H}_8\text{N}$ for cinchonine and cinchonidine, and $\text{C}_9\text{H}_8(\text{OMe})\text{N}$ for quinine and quinidine, and carbon atom (4) is no longer asymmetric. It follows that the difference in optical activity in these bases, and therefore in the four alkaloids from which they are derived, depends on the arrangement of groups round carbon atom (3) and is different in sign in the two pairs.

It is thus possible to divide the cinchona alkaloids into two series, a dextrorotatory and a laevorotatory :—

Chemical Name	Natural Alkaloid	Corresponding hydroalkaloid
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Cinchonine Series—Dextrorotatory Alkaloids

Cinchonine	Cinchonine	Hydrocinchonine
Hydroxycinchonine	(Cupreidine—unknown)	Hydrocupreidine
Methoxycinchonine	Quinidine	Hydroquinidine

Cinchonidine Series—Laevorotatory Isomerides

Cinchonidine	Cinchonidine	Hydrocinchonidine
Hydroxycinchonidine	Cupreine	Hydrocupreine
Methoxycinchonidine	Quinine	Hydroquinine

Acton (1922) believes that the pharmacological properties of the two groups also show a divergence, which is dependent on three factors in the structure of the complex alkaloid molecule :—

I. The grouping of the quinuclidine system round the asymmetric atom (3). The dextrorotatory alkaloids are more powerful in their effects than the laevorotatory alkaloids of the cinchonidine series, as

shown by their toxicity to mice and to paramœcium, by their inhibitory action on enzymes, and by their effects on blood pressure and uterine muscle. The cinchonidine series act more powerfully as local anæsthetics.

II. The vinyl group ($\text{CH}=\text{CH}_2$) in the quinuclidine system. The natural alkaloids are rather more toxic to paramœcium than the hydro-alkaloids. The latter are more toxic to mice, inhibit enzyme action, and cause a greater fall of blood pressure and greater uterine contraction than the natural alkaloids.

III. The group R in the quinoline ring. The higher members of both series of the hydroalkaloids are more toxic to mice, paramœcium, bacteria and leucocytes, and are more powerful local anæsthetics. Their action on the inhibition of enzymes, on blood pressure and uterine muscle is reduced.

Considerable interest in the past few years has been aroused by the modified cinchona alkaloids, for with hydrogenation of the vinyl group and replacement of the methoxyl group of quinine and quinidine by higher alkyloxy groups, the following compounds are produced. When the alkyloxy group is

- OCH_3 there is formed Methylhydrocupreine.
- OC_2H_5 there is formed Ethylhydrocupreine (Optochin).
- $\text{OC}(\text{CH}_3)_2$ there is formed *iso*-Propylhydrocupreine.
- $\text{OCH}_2\text{—CH}(\text{CH}_3)_2$ there is formed *iso*-Butylhydrocupreine.
- $\text{OCH}_2\text{—CH}_2\text{—CH}(\text{CH}_3)_2$ there is formed *iso*-Amylhydrocupreine (Eukupin).
- $\text{O}(\text{CH}_2)_5\text{—CH}(\text{CH}_3)_2$ there is formed *iso*-Octylhydrocupreine (Vuzin).

Optochin is highly toxic to the pneumococcus, vuzin to *Corynebacterium diphtheria*, while both eukupin and vuzin have been used as dressings for septic wounds and are said to be powerful anæsthetics. Although Izar and Nicosia (1914) have recommended the use of optochin in malaria, it is actually much less effective and far more toxic than quinine. The same is true of eukupin and vuzin.

CHAPTER XVII

PHARMACOLOGICAL ACTION OF CINCHONA ALKALOIDS

To comprehend the rationale of the therapeutic action of these alkaloids it is important to have a clear idea of their general pharmacological action. The type of action produced by quinine closely resembles that produced by the other alkaloids and it can be taken as a typical example of this group.

Action on protoplasm. Quinine occupies a peculiar position among the vegetable alkaloids. While most of the other alkaloids have a more or less cleanly defined point of attack in the body, and act on special tissues, quinine acts as a general protoplasmic poison which in sufficient concentrations destroys all cells, including those in which purely vegetative processes take place. Its action is specially marked on leucocytes, amoebae and spermatozoa. The action generally begins with temporary stimulation of activity of the protoplasm, being quickly followed by inhibition of all vital processes and finally death. It has been shown that quinine, like saponins and proteins, tends to concentrate on the surface of solutions to such an extent as to form almost a rigid film (Ramsden). This interferes with the condensation of other substances at the surface and the catalytic phenomena, inorganic as well as organic, are hindered, resulting in diminished metabolism. The surface action is also demonstrated by the arrest of Brownian movement and there is a tendency to precipitate colloidal solutions such as proteins. Quinine may thus produce anaphylactoid phenomena. The quinine film probably decreases the permeability of the cell, thereby producing a narcotic action such as is seen on local application to nerve cells, muscle cells, etc. The inhibition of movements of the white blood cells, spermatozoa, infusoria, and ciliata, is probably due to the rigidity of the film formed. All these effects give this alkaloid the property of being a general protoplasmic poison. Its toxicity to vertebrates is however comparatively low; probably it is bound up or deposited in insoluble or harmless form in some of the tissues of the body.

Protozoa. If quinine is allowed to act on the undifferentiated protoplasm of such an organism as an amoeba its action is quite characteristic. The metabolic processes in the cell are retarded and this affects not only the anabolism but katabolism also. Minute doses therefore merely produce slowing of the activities in the organisms, while large doses produce first paralysis and then death. Very dilute solutions such as 1 in 20,000 to 50,000 destroy amoebae and paramoecia in a few hours

and some pathogenic protozoa, e.g., plasmodia. The protoplasm in amœbæ becomes granular, spherical and in a few hours nothing but granular detritus remains; this action occurs in the plasmodia in presence of the merest traces of quinine. Mice given a few daily injections of 5 to 6 mgm. of quinine are said not to be infected with nagana, although these doses will not free the infected mice from the parasites. Dourine is not influenced but the incubation period of rabies is prolonged by large doses. Bass and Johns in 1912 first cultivated the malarial parasite. Bass later showed that 0.005 c cm of a 15 per cent. solution of quinine dihydrochloride corresponding to 2 gm. in the blood of a person weighing 150 lbs., killed *P. falciparum* in 5 to 29 hours. The activity of certain forms of non-pathogenic spirochætae, amœbæ, etc., is inhibited at first and finally stops. Certain protozoa are however not affected by quinine at all; salt water amœbæ and spirochætae of relapsing fever are able to live in a 1 in 200 solution.

Bacteria. The toxic action of quinine on the protoplasm endows it with bactericidal power but the action of the alkaloid on cocci and bacilli is somewhat varied. Its germicidal efficiency is considered to be about half that of phenol, whilst its antiseptic action approaches that of mercuric chloride. A dilution of 1 in 2,000 delays growth of bacteria and 1 in 800 inhibits the growth in fluids of organic matter and prevents lactic and butyric acid fermentation. The drug also retards the action of many unorganised ferments.

Some organisms are very sensitive to quinine and its derivatives while it has little or no action on others. Moulds are most resistant to it, in fact, they thrive in solution of quinine sulphate. About 0.5 per cent. is required to stop the growth of putrefactive bacteria and 2 per cent. to kill them. Typhoid bacilli cannot grow in 1 in 30,000 solution. Quinine has no direct influence on the course of most bacterial infections whether given by injection or otherwise, the pneumococcus being an exception in this respect. Both quinine and related alkaloids when used in sufficiently large doses early enough have been successful in controlling experimental pneumococcal infection in animal and pneumonia in man. Some of the newer derivatives of cinchona, for example the cupreines, exert a powerful bactericidal action on certain micro-organisms even in the presence of proteins, and at the same time have a relatively low toxicity for the body cells. This action as a rule increases as we go up the series from ethyl hydrocupreine to iso-octylhydrocupreine. Thus quinine in 1 in 1,000 concentrations, ethylhydrocupreine in 1 in 2,500 and iso-octylhydrocupreine or vuzin in 1 in 60,000 concentrations, will destroy *B. tetanus*. The same is true of streptococcus, staphylococcus and *B. diphtheria* with some reservations. Below is a table showing the relative bactericidal action of quinine derivatives on some micro-organisms (Dixon).

Bactericidal action of quinine derivatives

	Diph- theria bacillus	Tetanus bacillus	Strepto- coccus	Staphylo- coccus	Pneumo- coccus
Quinine Hydrochloride	1--100	1- 1,000	1- 1,000	1-500	1- 2,000
Ethyl Hydrocupreine Hydrochloride (Optochin)	1-400	1 2,500		1-500	1 -400,000
Isopropyl-hydrocupreine hydrochloride	1- 800	.	1--8,000	1-1,000	1-200,000
Isoamyl hydrocupreine hydrochloride (Eukupin)	1-2,000	1- 20,000	1-40,000	1-8,000	1-20,000
Heptyl hydrocupreine bihydrochloride ..	1-8,000			1-64,000	
Isooctyl hydrocupreine (Vuzin) ..	1-8,000	1--60,000	1-80,000	1-6,000	
Eucuprinotoxin ...			1-60,000	1-52,000	

The corresponding series of cupreidine compounds have similar actions.

Ethyl hydrocupreine known under the trade name of Optochin has a very high degree of toxicity for the pneumococcus, 1 in 400,000 solution having a destructive effect on this organism *in vitro*; 1 in 800,000 solution in serum inhibits the growth of pneumococci. Strains of pneumococci and also streptococci are inhibited *in vitro* by 1 in 100,000 solution whereas meningococci and gonococci require a strength between 1 in 10,000 to 1 in 5,000. This selective action of the drug led to its trial in pneumococcal septicaemia produced in rats and guineapigs, but the results were not conclusive. To get a bactericidal action it was found necessary to give 0.024 gm. per kilo. body weight in 24 hours, and for an average man this will mean a dose of just over 1.5 gm. Doses of 20 to 25 grains in 24 hours render the blood toxic to pneumococci but such effects of quinine as contraction of the field of vision and amblyopia, which are met with in therapeutic doses, are much more marked in the case of ethyl hydrocupreine and even such small doses as 8 grains have produced optic atrophy with permanent blindness. Further trials of this drug in man were therefore not proceeded with. Doses of 0.5 gm. in the treatment of pneumonia caused total blindness in some individuals, while in others vision partly returned. Pathological changes in the retina consist of white patches of necrosis, narrowing of blood vessels and sclerosis, as evidenced by depigmented areas. A combination of injury to the optic nerve, the retina and the choroid appears to be a peculiarity

of this drug. Susceptibility to these effects varies in different individuals. Besides it should be remembered that when the infection is at its height, the toxins have already had time to affect the tissue cells and mere destruction of pneumococci will be of little value. Bactericidal tests on different types of pneumococci show that in dilutions of 1 to 2 millions, ethyl hydrocupreine hydrochloride (optochin) kills type 3 of this organism; quinine arsenate does the same in 1 in 200,000 to 1 in 100,000, quinine sulphate 1 in 200,000 to 1 in 20,000, quinine hydrochloride 1 in 200,000 to 1 in 100,000 dilutions. The inhibiting effect of quinine on the pneumococcus is even greater than its germicidal power. Quinine hydrochloride and dihydrobromide exert a marked neutralising action on the toxicity of pneumonic lung extracts, prophylactic injections prolonging the life of animals 5 days or more, after injection of one M.L.D. of the extract, while quinine and urea hydrochloride and optochin afford little or no protection. The protective value of antipneumococcic serum in animals has been shown to be increased by the simultaneous injection of optochin and to a lesser extent by other quinine compounds.

Iso-octyl-hydro-cupreine or vuzin. This compound was extensively employed by the Germans during the War for disinfecting suppurating gunshot wounds, owing to its remarkable bactericidal action on streptococci and tetanus bacilli in very high dilutions (1 in 80,000 and 1 in 60,000 respectively). It was used in strengths of 0.1 gm. in a litre of water and proved to be very efficacious. It is also effective against the micro-organisms responsible for gas gangrene. Iso-heptyl-hydrocupreine is especially destructive to staphylococci.

Iso-amylhydrocupreine (Eukupin) has been found to have a specific effect against vibrios and diphtheria bacilli. It has been tried in Vincent's angina, and it is useful in other forms of ulceration, e.g., Cachar or Naga sore. Both 'vuzin' and 'eukupin' are readily absorbed, but act more slowly than quinine when administered to man by the mouth.

The destruction of the micro-organisms is probably brought about by the combination of these alkaloids with the protoplasm of the bacteria, and their varying qualitative efficacy against different micro-organisms can be accounted for by the difference in their affinity for them. The bactericidal action of the alkyl derivatives of hydrocupreine is more or less similar to that of quinine, but they are much more toxic.

External action. Quinine solutions applied to the unbroken skin do not produce any disagreeable sensation. Rashes are however frequently produced in workers in quinine factories after prolonged exposure to the drug and certain local irritation is set up. Quinine and its salts are not absorbed by the intact skin except under the influence of an electric current. They are however taken up rapidly by the mucous membrane.

Alimentary system. When taken by the mouth quinine acts as a bitter, stimulates the gustatory apparatus and improves the appetite; the peptic glands are reflexly stimulated. In the stomach it is dissolved by the hydrochloric acid but it has no direct action on the flow of the gastric juice. Given by the mouth there is little difference between soluble and insoluble salts, as the alkaloid is converted into soluble hydrochloride and the less soluble salts are made more soluble by the gastric acid. Passing into the duodenum, it is usually absorbed rapidly. After absorption quinine circulates in the blood as quinine base. The absorption occurs mainly from the small intestines and it is rapid and complete. The largest amounts are absorbed during the first six hours after administration of a dose. Only a small amount is taken up from the stomach when it is given on a fasting stomach and in the form of a soluble salt; a relatively smaller amount is absorbed from the large intestine. Absorption is retarded if quinine is given with or soon after food. The soluble salts of the alkaloid are absorbed a little more quickly than the insoluble ones, for compounds like equinine and quinine tannate have first to be hydrolysed by the alkali of the duodenum before they are absorbed.

Ferments. Interference with the activity of ferments is a well-marked property of quinine and its inhibiting action on oxydases in the blood is well known. The acidification of shed blood is slowed. Freshly excised still-living kidneys, perfused with blood containing glycocoll convert benzoic acid into hippuric acid; if however minute traces of quinine are added to the blood this synthesis is prevented. It seems likely that the chief effect of quinine on the living organism is to restrict many of the normal chemical changes—synthesis, oxidation and decomposition and in this way to diminish the metabolism (Schmidberg). These effects are probably due to the paralysing action of quinine on the intracellular enzymes by whose aid the chemical changes are brought about. It is doubtful if the concentrations of quinine, in therapeutic doses, rise so high as to hinder action of oxydases in the body. All the metabolic processes in the body, whether of anabolic or katabolic nature, are decidedly inhibited and tissue waste and energy production are both retarded.

Various digestive enzymes are affected to varying extents according to the degree of concentration of the alkaloids. Acton (1921) studied the action of cinchona alkaloids on these enzymes *in vitro* and found that the activity of ptyalin, the starch digesting ferment of the saliva, was completely inhibited by the acid salts. As the digestion of starches is over in 10–30 minutes, no interference will result if the alkaloids are given half an hour after a meal. Peptic inhibition is more marked with the cinchonine series and the inhibition is less when the ferment first attacks the protein than when the protein is first acted upon by the alkaloids. On the tryptic digestion, quinidine has a more powerful

inhibiting action than quinine; the action of pepsin is retarded in the presence of a 1 in 5,000 solution of quinine or quinidine. The deduction of practical importance that can be made from these experiments is that, as the inhibition of peptic digestion is bound to lead to deficient peptone formation, the time of administration of these alkaloids in relation to meals is of the utmost importance. They should be administered when they least interfere with the activity of the digestive enzymes, that is about 1½ to 2½ hours after meals.

Circulatory system. *Action on the blood: Leucocytes.* If quinine is given intravenously in large doses to an animal, certain changes are noticed in the blood corpuscles. The leucocytes lose their amoeboid movements, become round and granular, diapedesis through the capillary walls ceases and the coagulation time of the blood is reduced. Even in very low concentrations (such as those occurring in the blood after administration of therapeutic doses of quinine) the movements of the leucocytes are inhibited and diapedesis is stopped. This can be demonstrated in the exposed mesentery of the frog. The number of white blood corpuscles in man is reduced to half the normal number per c.mm. of blood or even less, after administration of a dose which is 1/20,000 of the body weight, lymphocytes being chiefly affected. This leucopenia is often preceded by a preliminary leucocytosis in which chiefly the polymorphonuclears are concerned. For these reasons quinine is said to counteract inflammation and suppuration and is recommended in catarrh of the nasal passages.

Erythrocytes. On the erythrocytes, the acid salts of quinine have a decidedly hæmolytic action *in vitro*, and blackwater fever has been attributed by some to the toxic effects of quinine salts on the red blood cells. Rarely, ecchymosis may occur in the tissues after administration of quinine, probably from injury to the erythrocytes leading to the formation of thrombi, or from injury to the walls of the small vessels. The hæmoglobin shows a characteristic change with strong solutions of quinine. Neither acid hæmatin nor methæmoglobin is formed; uazin has similar action.

It has already been stated that quinine circulates in the blood as quinine base. Acton has demonstrated that strong solutions of quinine and quinidine base such as 1 in 2000 in normal saline, produce no hæmolysis of washed red corpuscles *in vitro*, even after incubation for 24 hours. In the case of acid salts, such as the bisulphate, there is faint hæmolysis in 1 in 8000 solution, but none whatever in 1 in 11,000 dilution. Intravenous injections of strong solutions of acid salts are therefore highly undesirable and there is no doubt that rigors, which are sometimes observed after such injections, are due to the hæmolysis thus produced. As a matter of fact, injection of acid salts of quinine and other cinchona alkaloids, whether intravenous or intramuscular, is not justifiable from a physiological point of view, as those alkaloids circulate in the blood as bases. The acid salts are preferred

merely because they are soluble and therefore convenient for administration.

Blood pressure. The blood pressure is definitely lowered after intravenous injection and Acton has pointed out that this depression is much more marked with the dextro-rotatory cinchonine series, quini-dine being the worst offender in this respect. His experiments show that it causes a much bigger fall, the effects are more prolonged and therefore it should not be given by this route.

Action on the heart. The heart muscle is acted on in the same way as the other muscular tissue. Very small quantities accelerate the pulse and raise the blood pressure ; large quantities produce the reverse effect, the action is directly on the motor apparatus of the heart and not on the nerves. The depression of the heart is no doubt responsible for the collapse produced by very large doses in patients suffering from fever. Quinine depresses isolated strips of the heart of a turtle. A frog's heart is weakened by 1 in 50,000 solution, and 1 in 5,000 stops the heart in diastole in a few minutes (large doses of digitalis stop the heart in systole). It is for this reason given in irritable conditions of the myocardium.

Quinine is considered by some authorities to be the greatest regulator in arrhythmia due to extra-systole including auricular fibrillation. It has been combined with digitalis in cardiac diseases for over a century. Quinine and digitalis are given not only where arrhythmia is present, but also where large doses of digitalis seem urgently needed and where concomitant disturbances make quinine desirable. Quini-dine, a dextro-rotatory isomer of quinine, has lately been the subject of much study owing to the beneficial effects it produces in auricular fibrillation and arrhythmia. By fibrillation is meant an inco-ordinated, tremulous flickering movement of the muscle wall of the auricle. A circus movement having its path about the mouths of the great veins, has been shown to be the basis of the disordered mechanism of fibrillation and flutter of the auricles. The fibrillation of the auricle may amount to 500 a minute while the ventricular rate may be 120 to 140 and in rare case 200 per minute, because many of the impulses fail to excite any ventricular contraction. The relief afforded by quini-dine is believed to be produced by the depressant effect of the alkaloid on the heart muscle which prolongs the refractory period of the auricular muscle, in this way ending the circus movements. This reduces the excitability of ventricles and auricles to a point below that at which fibrillation is possible. Most of the cinchona alkaloids lower the contractibility of the cardiac muscle. Intravenous injections of therapeutic doses in animals, 10 to 15 mgm. per kilo. corresponding to 5-10 grains in man, produce the following effects:—(1) It prolongs the refractory period of the cardiac muscle and slows conduction. (2) It depresses the excitability of the cardiac muscle, i.e.,

raises the threshold of stimulation and greater resistance to extra-systoles. (3) It lowers the rate of sinus impulse discharge. (4) It mildly depresses the vagus. (5) It produces a slight decrease of auriculoventricular conduction. (6) It increases amplitude of excursions by 16 to 100 per cent., due to greater diastolic filling resulting from longer diastolic pause. (7) Temporary fall of the systemic blood pressure and rise in the pulmonary blood pressure occurs. (8) Inconstant effect on the T-waves and inconstant alteration in response to vagus stimulation are produced.

The chief criterion for its use is a healthy myocardium. The following points may help in the selection of suitable cases:--

(1) Fibrillation of recent onset. (2) Slight dilatation of heart. (3) Absence of valvular disease. (4) Fibrillation associated with acute infection, *e.g.*, influenza. (5) Hypertrophied heart. Unsuitable cases are those with:—(1) Enlargement and valvular disease, and hearts which after rest and digitalis do not elicit evidence of reserve strength. (2) History of embolism. (3) Idiosyncrasy to cinchona derivatives. (4) Cardiac pain.

In human beings it is usually given by the mouth in the form of sulphate either in tablets or in capsules. A dose of 0.2 gm. is given on the first day and if it is well borne, it is increased next day to 0.4 gm., three or four times a day, but not exceeding the total of 2 gm. per day. If no benefit follows within 3 days, quinidine is generally not likely to do good. In the case of success the drug is omitted and readministered on recurrence of symptoms. The maintenance dose is 0.25 gm. per day. Intravenous injections are dangerous as the margin of safety is small. In about 50 per cent. of the cases the medication has no effect, and these are generally the advanced cases of heart disease with extensive changes in the myocardium. As the drug has a paralysing effect on the heart muscle, it should be given with caution and after a course of digitalis in cases of failure of compensation. Onset of frequent miniature beats or a persistently high ventricular rate are indications for cessation of treatment. In carefully selected cases the use of quinidine in cardiac irregularities is justifiable, important contra-indications being a high grade of myocardial damage. Lewis has suggested that in changing the rhythm there may be ventricular standstill for sufficiently long periods to cause death. Previous digitalisation increases the chance of success and diminishes the danger of accidents. Toxic doses impair the heart, producing sino-auricular or auriculo-ventricular block, ventricular fibrillation or gradual inhibition of the whole heart. In this case the auricles usually stop before the ventricles. In susceptible individuals quinidine may produce phenomena of hyper-susceptibility, giving rise to nausea and flushing. Rarely, quinidine may change the intra-auricular block and

fatal ventricular fibrillation may occur. As quinine and quinidine are rapidly excreted the drugs do not give rise to any cumulative effects.

Respiration. Given intravenously, these alkaloids have a depressing effect on the respiratory centres. Hydrobromides have a much weaker effect in this respect than the hydrochlorides and therefore these are preferred for intravenous administration. It has been shown that after lethal doses in cats (25 mgm. per kilo. body weight) the heart continues to beat for two minutes after stoppage of respiration.

Central nervous system. On the cerebrum, quinine has a depressing effect, though not to such a marked degree as some of the other antipyretic drugs. Because of its sedative action on the central nervous system it has been used to induce sleep, a few grains being given at bed time. Large doses may produce mental excitement such as that manifested in cinchonism. When taken for prolonged periods it may give rise to psychical derangements, which take the form of defective associative processes, flight of fancy, but these are never very marked. In rare cases loss of consciousness has been seen, accompanied by delirium, convulsions and death following symptoms of collapse. Weakening of the heart is the main cause of death, but respiration stops before the heart. Death has been recorded with a 2 gm. dose but as a rule fatal dose is 8 to 10 gm. or more. As quinine is rapidly excreted, recovery generally takes place, but deafness and defect in the sight may remain for weeks or even months. In ordinary therapeutic doses it has no effect either on the medulla or on the cord, but large doses depress these structures and the respiratory centre is especially attacked. Very large doses produce paralysis of the whole central nervous system, leading to stupor, coma and death.

Peripheral nerves. The cinchona alkaloids and their derivatives produce a slow and prolonged abolition of sensation by their direct effect on the sensory nerve endings. For this reason quinine is not infrequently employed in the treatment of neuralgia. Lately, a good deal of attention has been paid to their power of producing local anæsthesia and their potency can be judged from the fact that while 1 in 50 solution of cocaine hydrochloride will produce anæsthesia of the cornea of a rabbit, the same effects can be produced by 1 in 60 of quinine hydrochloride, 1 in 100 of hydro-quinine, 1 in 1000 of ethyl hydrocupreine (optochin) and 1 in 1200 of iso-amyl-hydrocupreine.

Strength of solutions of cinchona derivatives producing corneal anæsthesia :—

Quinine HCl	1 in 60
Cocaine HCl	1 in 50
Hydroquinine HCl	1 in 100
Ethyl-hydrocupreine (optochin)	1 in 1000
Iso-amyl-hydrocupreine	1 in 1200
Eucupinotoxin	1 in 2000

The cupreidine series have a similar though slightly less marked action. Quinidine and cupreidine compounds have also great anaesthetic properties but their action is somewhat weaker.

Quinine is often combined with urea and is used as a local anaesthetic. This combination increases its solubility and its power of penetration into the cells, but the resulting compound is decidedly weaker and has to be used in twice the strength necessary if quinine alone is used. As a rule 0.25 to 1.0 per cent. solutions are quite effective. In lumbago 5 c.cm. of a 1.0 per cent. solution injected into a muscle may relieve the pain. The disadvantages of the cinchona derivatives in comparison to cocaine and its allied compounds are that (1) injections are painful; (2) the induction of anaesthesia takes longer; (3) they are more irritating and in stronger solutions may cause infiltration of the tissues and sloughing; (4) the anaesthesia produced may last for several days. These compounds also irritate the conjunctiva and their action is not deep-seated; otherwise they would be excellent anaesthetics for ophthalmic operations.

Special senses: *The eye.* Quinine and its allied compounds, when given in toxic doses, produce visual disturbances such as contraction of visual fields, diminution in acuity of vision, colour blindness leading to amblyopia and amaurosis. The development of the blindness varies enormously, some patients quickly become anauritic, whilst in others varying degrees of amblyopia supervene. The pupils are dilated and of sluggish reaction; there is central scotoma for green and red. Ophthalmoscopic examination of such cases shows constriction of the choroidal vessels; the retina looks pale and the disc hazy and oedematous. The constriction of blood vessels is probably of vaso-motor origin and it is much more marked with such derivatives as optochin; later the vessels become dilated, thirty grains of quinine taken in one dose may bring about this condition but therapeutic doses as a rule produce little effect. With large doses temporary and permanent blindness have been known to occur, probably from the effect of the drug on the nerve fibres of the ganglion cells. Generally a speedy recovery is to be expected, but in many patients the central vision is permanently damaged and in addition the light sense remains defective and the visual fields remain contracted. Colour vision may be considerably regained; a certain amount of dilatation of the pupils may remain. It is believed that most of the visual disturbances in patients taking ordinary therapeutic doses of quinine in malaria are due to parasitic emboli in the retinal vessels and not to the effect of quinine on the retinal elements. Treatment of such patients consists in giving strychnine which is a direct stimulant to the optic nerve fibres, and inhalation of amyl nitrate and oral administration of 2 grains of sodium nitrite daily, with a view to dilating the blood vessels. Digitalis and bromides have also been recommended.

The ear. The common accompaniments, ringing in the ears and deafness appear to be chiefly due to congestion of the blood vessels. Sixty grains in 24 hours may cause marked disturbances in the ear and even deafness. In rabbits congestion and ecchymosis in the internal ear were produced by giving large doses of quinine. Degenerative changes have also been noticed in the cochlear ganglia; otitis media may be set up by long-standing congestion, and permanent deafness may be produced. When giving quinine to patients with middle ear disease, the possibility of its activating a quiescent condition should be borne in mind.

Quinine has a specific action upon the special sense organs, the first sign of an overdose being ringing and roaring in the ears, accompanied by slight deafness. At the same time the eyes are affected, and there is diminution in the field of vision, photophobia and even temporary blindness. The effects are due to the action of quinine on the nervous elements in these organs.

Metabolism. This is affected in a most remarkable manner by quinine in very small doses. There is a slight transient increase in the nitrogenous constituents of the urine followed by a marked decrease, especially in urea and uric acid. Quinine is said to cause diminution of heat-production by decreasing metabolism from its action on the muscles and glands. It inhibits both the anabolic and katabolic processes of the cell, the processes of oxidation being thus markedly reduced. For this reason, economy in the metabolism of the body as a whole is secured, especially in those conditions in which katabolism has been stimulated by pathological processes. After administration of quinine in febrile conditions, urea, uric acid, sulphates, phosphates and chlorides decrease in the urine. Some drugs diminish the excretion of urea, sulphates, etc., but their deficiency in the excretion of nitrogen and sulphur in this form is counter-balanced by the larger excretion of unoxidised substances containing nitrogen and sulphur, *e.g.*, ammonia, leucin, tyrosin, and cystin. This is not the case after quinine. The use of quinine therefore in wasting diseases such as tuberculosis, is said to be based on rationalism as it tends to check the excessive breakdown of proteins which occurs in these diseases. It is also significant that in spite of the fact that metabolism is diminished, the gaseous interchange, *i.e.*, the absorption of oxygen and the elimination of carbon dioxide remains unaffected. This means that some nitrogenous food, which normally is used up and later appears as a solid constituent of the urine is being stored in the body and the animal, being in equilibrium, is putting on weight.

Prior's experiments on himself and dogs showed that while the urine was increased 11–12 per cent., urea was decreased 19–20 per cent., uric acid 72 per cent., sodium by 9 per cent., sulphuric acid by 34 and phosphoric acid by 23 per cent. Hardikar (1920) however showed that quinine

has no effect on the protein metabolism in health, and in malarial fever it is not possible to control tissue waste and to husband energy by means of quinine.

Effect on the body temperature. In healthy individuals quinine produces no effect on the body temperature, but in most febrile diseases ordinary therapeutic doses of quinine produce a fall of temperature. It would seem natural to connect this antipyretic action with the depressing influence of the drug on metabolism which would thus produce diminished production of heat. But against this view is the fact that oxygen intake and carbon dioxide output are not materially altered. It has been shown, however, that oxidation is not the only source of heat production and that heat may be produced by the splitting and hydration of nitrogenous molecules, in the course of which nitrogen is converted into urea. In febrile animals the body temperature falls after quinine, even when all the increased loss of heat is prevented. Calorimetric experiments show that loss of heat from the body surface is diminished after quinine. The only possible explanation could be that the antipyretic effect is due to diminished production of heat. The action of quinine in this respect is the reverse of other antipyretics, such as those derived from the coal tar. The reduction of temperature after quinine has therefore been likened to letting the fire burn low or go out in a room that is too hot, while to give antipyretics of the coal tar groups is to open the windows. The fall of temperature runs a course parallel to the nitrogenous metabolism, as measured by the excretion of nitrogen in the urine. Quinine would therefore be a very useful drug in this respect. In the presence of fever it is also said to produce hyper-glycæmia and to lower excessive concentration of the blood.

According to some observers, after small doses of quinine there is a slight rise of temperature before the usual fall; there is a corresponding increase in nitrogen excreted in the urine. This may be compared to the preliminary stimulant action of the dilute solutions on infusoria or white corpuscles, before paralysis.

Muscle. Quinine first causes a temporary increase and then a decrease in the absolute strength and the working capacity of muscle and finally death followed by immediate rigor. Dilute solutions hasten fatigue. The results are the same whether a muscle is curarised or not; the action is therefore on the muscle fibres, irrespective of their nerves. On smooth muscle the effect is similar. The total effect on muscle tissue with therapeutic doses is small. Quinine is however said to be a tonic, a word which is often abused. This term should be limited to drugs which increase the tone of muscles, *e.g.*, strychnine, but quinine is not one of these. The term is commonly employed to denote remedies which improve the general health and vigour of the patient.

Uterus. Quinine has often been employed to increase the force of contractions in the second stage of labour, under the belief that it favours the contractions of uterine muscle; it is also believed that given in large doses it has an ecbotic action. The action appears to be directly on the muscle fibres without the intervention of the nervous system, as atropine does not modify its action. According to some observers quinine inhibits the non-gravid uterus and stimulates the gravid uterus, because the distension of the fibres has rendered them sensitive to any kind of stimuli. It should be remembered that high temperature, which often accompanies malaria may in itself produce death of the foetus and evacuation of the uterus. Temperature in pregnant women suffering from malaria should not therefore be allowed to go above 103°F. Experiments on isolated pregnant uteri of rats and guinea pigs show that in dilutions of 1 in 300,000 quinine produces no effect whatever, 1 in 150,000 only produces contraction under certain circumstances and 1 in 44,000, a concentration which can never be attained in the blood unless the patient is literally poisoned with quinine, produces a tonic spasm of both the circular and longitudinal fibres, which if maintained kills the foetus. Dilution of 1 in 10,000 to 1 in 5,000 may produce relaxation and paralysis. Concentrations of 1 in 150,000, such as occur in blood normally after ingestion of quinine in moderately large doses, stimulate the intermittent contractions. If now some exciting cause is present such as weak membranes or a patulous os, the membranes may rupture and labour may be started. There is disagreement regarding the effect of quinine on the tone of the uterine muscle. According to some authorities a considerable increase of tone is produced but the action is not sufficiently strong to produce a tonic contraction dangerous to the foetus.

Spleen and intestine. In animals under anaesthesia injections of quinine produce a marked reduction in the volume of the spleen. In pathological enlargements of this organ such as those occurring in malarial fever, administration of quinine causes contraction and reduction in its size. These effects are probably brought about by the contraction of the involuntary muscle tissue in this organ. The intestine may also be contracted.

Fate in the body. Quinine is easily absorbed from the mucous membrane, subcutaneous and muscular tissues and it circulates in the blood as quinine base. The length of its stay in the blood is very short. When quinine is given in large and continuous doses by mouth, a concentration in the blood of from 3 to 10 mgm. per litre can be obtained. Doses of 2 gm. a day must be given to obtain a concentration of 10 mgm. per litre in the blood; and when the concentration rises above this, severe symptoms of cinchonism arise. An intravenous injection of 0.8 gm. of quinine gives a concentration of 200 mgm. per litre, but the drug is rapidly removed from the blood. Of the quinine present in the blood, some is in the blood corpuscles and some in the

serum. A large proportion (about 60 per cent.) is deposited in such organs as the liver, gall bladder, kidney, supra-renals, lungs and spleen. In the liver, the quinine molecule is split up and the drug is partly destroyed. The quinine which escapes destruction in the liver and other organs, passes through the circulatory system and is eliminated as quinine base in the urine. Up till now no other recognisable derivatives have been detected. There has been difference of opinion as regards the distribution of quinine among the constituents of the blood. After absorption, the salts of quinine are carried in the blood in small amount and rapidly deposited in various tissues, the supra-renals and the kidneys receiving the most; the lymph glands and muscle tissue do not contain any and the red blood cells very little. The following distribution of quinine in different organs has been given by Ramsden :- Serum 0.1326 mgm., corpuscles 0.005 mgm., liver 14.85 mgm., kidneys 4.025 mgm., supra-renal 7.02 mgm.

Quinine occurs in the lungs in fairly large quantities. Experiments show that after ingestion per os or by injection, guinea-pigs show a much greater proportion of quinine in the lungs than in the liver. This is also the case with optochin and for that reason these compounds were recommended in pneumonia. Studies by Hatcher and Weiss (1927) show that in cats and dogs, 95 per cent. of quinine disappears from the blood in about 5 minutes, after intravenous injection but traces may be found as long as 15 hours afterwards. The alkaloid is fixed by the capillaries immediately after the injection, and they probably play an important part in returning it to the circulation. It is promptly fixed by the lungs, liver, heart, kidneys and brain in higher concentration than the average for the remaining portion of the body; it is given up rapidly so that after 3 hours scarcely any trace of quinine can be found in these organs. It is suggested that fixation by the capillaries leads to more intimate contact between the protozoa affected and the alkaloid.

Morgenroth's observation showed that quinine is preferentially taken up by the red blood corpuscles, and in that position either kills the intra-corpuscular parasites or exercises a repellant action on the merozoites which are prevented from penetrating them and therefore perish. Other workers have also confirmed the storage of quinine in the red corpuscles. It will be seen therefore that there is no agreement among observers, regarding the ratio of quinine between plasma and red corpuscles while the drug is circulating in the blood. This is due to the fact that the technique of deciding this problem is extremely difficult and liable to error. King and Acton (1921) showed that the plasma and the corpuscles contain an equal amount. *In vitro*, experiments by Akashi (1923) show that the amount of quinine stored varies with the concentration of the alkaloid, number of red corpuscles and temperature. In the presence of much carbon dioxide the cells do not store quinine; the

liver cells also behave like red corpuscles. A certain proportion of quinine ingested is metabolised; the liver has been known to destroy morphine, nicotine and other alkaloids and probably it deals with quinine in the same way. It is moreover not known whether the quinine, which is stored up and metabolised in the organs, takes any part in the destruction of the parasites. Most observers consider that it does not; according to them the only useful portion of the dose is the portion which escapes destruction in the organs and circulates in the blood. The object of quinine treatment is to attain as quickly as possible a high concentration in the blood. Clinical observations have shown that to give a dose of quinine intravenously at the correct time is the quickest and surest way of curing an attack of malaria and of causing the parasites to disappear from the peripheral blood. The action of intravenous injections is however fleeting and these should be repeated at suitable intervals.

Excretion. Of the amount taken up by the body, the greater part ($\frac{2}{3}$ to $\frac{3}{4}$) is destroyed, probably by a thermolabile ferment found in the liver; most of the remainder is excreted unchanged in the urine. Small amounts pass out with the bile and traces may be found in the sweat and saliva. Quinine is thus excreted almost entirely by the kidneys. When given by the mouth small quantities occur in the faeces, but this is due to deficient absorption. By the kidneys it is excreted unchanged and if this organ is healthy the process is very rapid, quinine appearing in urine within 20 to 60 minutes of administration by the mouth on an empty stomach. The excretion reaches its maximum in three to five hours, and this maximum rate is maintained for 3 to 4 hours, after which it diminishes. The excretion is complete in sixteen to forty-eight hours. During continued administration of large amounts, elimination keeps pace with the administration, if the daily dose is not more than 30 grains (2.0 gm.). About 40 per cent. of quinine taken is excreted in the urine, and of this quantity two-thirds is excreted in the first 12 hours, and most of the remaining third within the next 24 hours; after 36 hours only traces are detected. Sixty per cent. of the drug which is not excreted in the urine is broken up and destroyed in the body.

There is difference of opinion regarding the influence of the form of administration, division of dose, etc. on the rate of excretion of the drug. According to some the action of quinine is more rapid with soluble salts, but Giemsa has shown that this is only true after injection. Soluble salts like quinine bihydrochloride and insoluble salts like quinine sulphate are excreted at the same rate in the urine. The amount of quinine excreted and rate of excretion of the alkaloid are the same whether the drug is given by the mouth, intramuscularly or intravenously. The consensus of opinion is that large spaced doses are most efficacious; that the greatest concentration in the blood is reached in about six hours and the maximum therapeutic effect somewhat later. It has

been variously stated that excretion or destruction is increased during fevers. In severe nephritis and in cardiac decompensation none may be excreted. It is now agreed that much of the drug is destroyed and that the remainder is excreted unchanged by the kidneys. The idea that part was converted into chinicine (quinotoxin), which is formed when quinine is heated with organic acids, is abandoned. Quinine is considered by some authorities to have a well-marked diuretic effect by its dilating effect on the kidney vessels. It is said therefore to be useful in certain forms of œdema and dropsy, especially those due to anæmia and cachexia.

The quinine concentration in the blood remains constant 4 to 8 hours after intramuscular and 2 to 12 hours after intravenous injection, as the excretion during this period shows no fall. The excretion rate falls after the first day. In malaria, the excretion rate is similar to that in health but variations are greater after oral administration.

CHAPTER XIX

THERAPEUTICS OF CINCHONA ALKALOIDS

The use of cinchona in the treatment of malaria dates as far back as 1657. The ship surgeons who visited India from 1657 to 1804 used cinchona bark in the treatment of ague. From 1804 to 1847 the cinchona bark treatment of fevers was entirely abandoned in India and treatment by purgatives such as calomel, and venesection was resorted to. In the meantime Pelletier (1820) discovered quinine which then was a mixture of all the alkaloids of cinchona bark. Subsequent to this the use of the bark declined and quinine sulphate gradually took its place. In the meantime other alkaloids such as cinchonine, cinchonidine and quinidine were discovered, and in 1866 the Madras Cinchona Commission was appointed to test their relative merits in the treatment of malaria. The tests were rough and mostly clinical and the Commission came to the conclusion that quinine was preferable to the other alkaloids. Next MacGilchrist (1914) tested a number of these alkaloids clinically, and he placed them in the following order from point of view of their anti-malarial efficiency:—(1) Hydroquinine hydrochloride, (2) Cinchonine sulphate, (3) Quinine sulphate, (4) Quinidine sulphate, (5) Optochin hydrochloride, (6) Cinchonidine sulphate, (7) Quinidine. Acton (1920) found dextro-rotatory alkaloids (except cinchonine) more toxic to *P. caudatum* than their laevorotatory isomerides. The corresponding hydro-alkaloids were less toxic. Further, the degree of alkalinity of the environment is of very great importance. The decision as to which alkaloid should be employed rested between hydroquinine, quinine and quinidine. Later experience showed that quinidine has a depressant action on the heart and in some patients untoward effects were produced by it. Cinchonine is a toxic alkaloid and produces irritation of the gastro-intestinal tract and symptoms of cinchonism. Cinchonidine was the least toxic of all and in ten

grain doses was quite effective against malaria. A combination of these alkaloids such as that occurring in 'cinchona febrifuge' or tota-quina was just as effective in the treatment of malaria as quinine. Sinton (1924) showed that in malaria there was some evidence of acidosis and therefore he advocated large doses of alkalies along with quinine.

QUININE IN MALARIA

As a curative agent. Quinine still holds the foremost position in the treatment of malaria, though the antimalarial value of the other alkaloids of cinchona bark is being more and more appreciated. In considering the relative therapeutic value of the different alkaloids it is of great importance to take into account their effect in causing harm or inconvenience to the patient. It may be said in favour of quinine, that it can as a rule be given in sufficient doses and for a sufficiently long period without fear. Cinchonine is more nauseating than quinine and is liable to produce nausea and blurring of vision. Quinidine is also more nauseating and has a powerful depressant action on the heart. Cinchonidine is neither very toxic nor irritating, but it is distinctly the weakest of the four chief alkaloids. Ethylhydrocupreine, although it has a powerful action, has a marked tendency to produce blindness. Quinine is therefore to be preferred.

There is still a considerable difference of opinion regarding the methods of administration, dosage and duration of treatment. This is largely due to the varying incidence, severity of infection and the resisting power of the several varieties of malaria in different parts of the world. It is therefore very difficult to lay down any hard and fast rules regarding these points, which may be of universal application.

The following main principles may be laid down in the treatment of malaria with quinine.

1. The alkaloid should be administered immediately after the diagnosis of malaria is assured, irrespective of the stage of the disease and the height of fever.

2. Quinine should always be given by the mouth when it can be administered and absorbed by that route.

3. The administration of the alkaloid must be continuous over a period of at least 5 to 10 days. Some authorities recommend considerably longer courses but these appear to be unnecessary.

4. Quinine will not act efficiently if the liver is sluggish or congested, or if the gastro-intestinal tract is disordered. To obviate these difficulties a brisk purgative, *e.g.*, 2 to 5 grains of calomel or an ounce of castor oil should be given on the day on which the quinine treatment is begun. Quinine should preferably be given in the form of solution and should be well diluted rather than in a concentrated form. This will aid absorption and will prevent its upsetting the digestive functions. If tablets or pills have to be given they should be crushed and given with plenty of fluid. The patient should remain in bed during treatment.

5. The administration of quinine should be so timed that it reaches the blood stream at the moment when the latter is at its alkaline tide. According to Acton and Chopra (1928) the portal blood stream reaches its maximum alkaline tide some $2\frac{1}{2}$ hours after a meal.

6. The alkaloid should preferably be administered with alkalis as these tend to increase the absorbing power of the intestinal mucosa for cinchona alkaloids from the small intestine.

The treatment of the disease can be divided into:—

(a) Treatment of the attack.

(b) After-treatment.

(a) **Treatment of the attack.** The patient should be put to bed before the quinine treatment is started and he should be kept in bed for at least three days if not longer, however mild the attack may be. Twenty to 30 grains quinine should be given daily, divided into 2 or 3 doses, according to the weight and age of the individual. Some clinicians give the drug every six hours on the assumption that the action of a dose lasts for six hours. As the febrile paroxysm which follows sporulation of the parasites usually begins between 2 a.m. and 12 noon, it is held that doses should be given commencing at 12 midnight. Whatever method is adopted the parasites disappear from the

blood and the fever ceases within 24 to 72 hours, but the treatment should be continued for at least five days after the fever subsides. Sometimes, quinine cannot be given by the mouth owing to persistent vomiting, especially in pernicious cases. In such cases the best method of administration is by the intramuscular route. Fifteen grains given in this way produce cessation of vomiting and other acute symptoms within a few hours, and disappearance of parasites in 18 hours. Quinine can then be given by the mouth.

(b) **After treatment.** In the treatment of all cases of fever it should be remembered that it is wrong to continue giving large doses of quinine for many days if it is not producing any effect. Quinine does good quickly if it is going to be of any use at all. Whether treating ordinary cases of primary attack or of relapse, it is seldom necessary or advantageous to give 20 to 30 grains of quinine daily for more than 7 to 10 days. If the fever does not subside some other factor is responsible for its production and the treatment should be changed.

No clear indication however has yet been obtained regarding the method of treatment of malaria with quinine, which would bring about disinfection with a minimum quantity of the drug in a reasonably short time, so that a relapse does not occur. This is due to the fact that the virulence of different strains of parasites in different parts of the world and their reactivity to various drugs varies very widely. It is not reasonable therefore to expect that all cases will respond in the same way to a standard plan of quinine treatment. That is the reason why many different schemes of treatment have been evolved to suit different conditions. A large percentage undoubtedly get cured after quinine treatment for seven to ten days in India, a smaller percentage may require longer treatment. The percentage of uncured cases is said to be small. Cure is usually signified to mean freedom from relapse and from parasites in the blood, after the treatment has ceased for two months. In an endemic malarial locality this is difficult to establish, as reinfections are taking place. Benign tertian malaria is especially resistant to quinine treatment, and it is believed by some that nothing short of a three months' course in the non-malarial season and a four months' course in the malarial season (when reinfections are occurring) will be effective in destroying all the parasites. Such a scheme of treatment is however impracticable, harmful and is not recommended. It is preferable to give a 7 to 10 days' course after each attack.

The following plans have been suggested for prolonged treatment:—(a) 10 grains of quinine once daily, (b) 30 grains of quinine on each of two consecutive days, *e.g.*, Saturday and Sunday, each week, the amount being preferably taken in 4 separate doses, (c) 30 grains of quinine only once a week, *e.g.*, Sunday, in four doses per day, (d) 15 grains on each of two consecutive days, *e.g.*, Saturday and Sunday each week, (e) 15 grains of quinine only one day each week, *e.g.*, Sunday. The amount in the last two plans is taken in one dose and is suitable for mild attacks. The daily dose plan would appear to be the best as it is difficult to state on which day the parasites will appear in the circulation in sufficient numbers to produce a paroxysm. Ten grains given every day will probably be sufficient to destroy the parasites in the circulation. Larger doses given at longer interval may compensate, but the chances of paroxysms recurring are greater. Such doses may not prevent reinfection of the patient, and whenever it is possible these should be prevented by other means. James (1922) laid stress on the time of taking quinine and considers that success of treatment depends on this. The dose, he considers, must be taken 2 to 3 hours before the onset of the febrile paroxysms. If a relapse occurs the whole course including the 5 days treatment of the attack should be repeated. The removal of patients from an endemic area to a better locality is often helpful. Patients suffering from malaria who do not do well in tropical climates immediately start improving when removed to a better climate. It should be remembered that removal to a very cold climate may light up an infection and bring about a severe relapse.

A number of standard treatments of malaria with quinine have been suggested to suit various localities.

(1) Ronald Ross (1921) advises during the first two weeks, 15 grains of the hydrochloride or sulphate of quinine daily; then 10 grains daily for six days in the week for eight weeks making a total of 690 grains. Benign tertian infections yield rapidly to this treatment as regards the febrile attacks, but are more difficult to cure in the sense of preventing further relapses than the malignant tertian type. Twenty-four thousand cases treated by the Ministry of Pensions were cured by this plan.

(2) The United States Malaria Commission (1921) recommends 30 grains (2.0 gm.) quinine sulphate daily in 3 doses while the symptoms last and for 4 days after; this is followed by 10 grains every night before retiring for 8 weeks. This course is said to have cured 90 per cent. of cases in the southern United States where malaria is not so severe. In Palestine this course was insufficient to cure chronic cases. The Jamaica Tropical Diseases Conference did not consider it advisable to recommend this method for universal application.

(3) Hehir (1927) suggests a three months' course:—

First week—(a) In benign tertian, 30 grains on the day of the next expected attack, and on alternate days until 120 grains have been taken during the week.

(b) In quartan, 30 grains as before, and on every third day until 90 grains have been taken.

(c) In malignant tertian, as for benign tertian.

(d) In double benign and double malignant tertian, 30 grains daily for three days, and then 20 grains daily for another three days, none on the seventh day.

Thereafter the course is the same for all types.

Second week.—15 grains daily.

Third & fourth weeks.—10 grains daily, with 20 grains every 7th day.

Fifth to eighth week.—10 grains daily.

Ninth and tenth weeks.—5 grains daily, with 10 grains on two consecutive days each week.

Eleventh and twelfth weeks.—5 grs. daily, with 10 grs. once a week.

(4) In South Africa, Pratt-Johnson and Gilchrist (1921) advise 10 grains of quinine 3 times a day for three weeks, then 10 grains twice a day for one month followed by 10 grains once a day for two months. They found the relapse interval was 14 days in benign tertian and 12 days in malignant tertian cases; the crescents disappeared, on an average, in 15 days with 25 grains of quinine a day.

(5) Panama Canal Zone Standard course (1925) is more drastic. The patient is given a dose of 2 to 3 grains of calomel followed by a dose of Epsom salts before the treatment is started. Fifteen grains of quinine are given three times a day until the temperature settles down and is normal for 5 to 6 days. Then ten grains are given three times a day for 10 to 14 days. This course cured the vast majority of malignant tertian infections.

It is not advisable to give such large doses as 30 to 40 grains a day for more than a week or ten days whether treating primary infection or a relapse, as it upsets digestion, and prolongs convalescence. It is also said that doses of 15 to 20 grains twice a week greatly reduce the number and severity of infections by limiting parasitic development, and help to prevent severe symptoms and establish tolerance. Thirty grains daily for 3 weeks among the British troops in the Punjab gave a relapse rate of 6.5 per cent. but it interfered with digestion, metabolism, etc.

(6) Mayne and Carter (1919) give 800 grains as follows:—

40 grains of quinine sulphate for 5 days	...	200 grains.
20 " " " " 10 "		200 "
10 " " " " 20 "		200 "
5 " " " " 40 "		200 "
		<hr/>
		800 "

(7) Ochner advises 2 grain doses of quinine every two hours, day and night for 48 hours repeated after six days' interval. It is very troublesome, less efficient and relapses are more frequent.

These treatments when properly carried out will eradicate infection in ordinary cases when re-infections are prevented. In induced malaria complete disinfection has been produced with a dose not exceeding 40 grains.

Synergist of Quinine. Acton (1921) first recommended the association of alkalies with quinine, with the idea of reinforcing its action. He found that the toxicity of this alkaloid on paramoecium and bacteria was increased when the hydrogen-ion concentration of the medium was on the alkaline side. Sinton and Lal (1924) gave large doses of alkali to patients to produce such a condition in the body. They found by means of Sallard's clinical test of giving by the mouth, 4 gm. of sodium bicarbonate well diluted, then 2 gm. an hour later, followed by 2 gm. every half an hour and testing the urine with litmus till it becomes alkaline, that there was acidosis in malaria. Acton and Chopra (1925) showed that the administration of alkalies before quinine, increases its rate of diffusion through the mucous membrane of the intestines. By a previous administration of alkali the concentration of quinine in the mesenteric vessels can be greatly increased.

Alkaline mixture A.

Sodium bicarbonate	60 grains.
Sodium citrate	40 „
Water	1 ounce.

Quinine mixture Q.

Quinine sulphate	10 grains.
Citric acid	30 „
(Or Dilute Sulphuric Acid)	30 min.
Water	1 ounce.

All cases are given calomel and magnesium sulphate before the treatment; for the first day of treatment 3 doses of A are given at 7-30, 9-30 and 11-30 a.m.; half an hour after the last dose one dose of Q is given. At 6 p.m. a further dose

of A is given followed 15 to 20 minutes after by one of Q. For the next 4 days one dose of A is given three times a day at 7-30, 11-30 and 6-0 p.m., followed on each occasion by a dose of Q. For the remaining 2 days one ounce of A is given morning and evening followed 15 to 30 minutes after by a dose of Q. Controls were given mixture Q only but no alkali. The total quantity of quinine given in 7 days was 180 grains and the criterion of cure was non-appearance of parasitic relapse during 8 weekly examinations. Sinton (1930) expressed the opinion that a one-week course suffices in the majority of cases. Though a prolonged course of treatment gives a slightly higher rate of permanent cures, the difference is not sufficient to warrant the extra time or expense. He also recommends plasmoquin 0.015 gm. daily throughout the course, to be given after food. If a relapse occurs the whole course should be repeated for one week, and continued for a second week, with two doses instead of three. No plasmoquin should be given in malignant tertian cases, but in benign tertian the dose of plasmoquin should be increased to 0.02 gm. daily during the 14 days' course. In chronic relapsing infections, the three daily doses of A and Q mixtures are given during the first week, followed by two daily doses for two weeks, a total of 0.03 to 0.04 gm. of plasmoquin is given in two daily doses after meals. If this treatment is carried out properly not more than 1.0 per cent. should remain infected.

If the alkaline mixture produces gastric disturbances, 2 drachms of sodium citrate in 2 ounces of water is taken slowly. Eighty per cent. of 800 malignant tertian infections were cured in a week by 30 grains of quinine daily with alkalies, and it is said that crescents disappeared three weeks after the asexual cycle. Alkali treatment can be combined with cinchona febrifuge. In severe cases a dose of alkaline mixture followed by 1 ounce of quinine mixture 15 to 30 minutes later, may be given at once without waiting for the purgative, but in these cases alkaline treatment should be continued till the urine becomes alkaline. In severe cases of malignant tertian malaria, the amount of sodium bicarbonate may be increased to 90 grains dissolved in two ounces of water. With this treatment in

Sinton's series, 28 per cent. of benign tertian relapsed as compared with 40 per cent. without alkali treatment; whilst in case of malignant tertian the relapse rate was 15 per cent. as compared with 79 per cent.

Quinine and alkali-producing substances (citric acid is converted into an alkali in the gut) can be prescribed in one mixture especially for outpatients in which it is not possible to carry out Sinton's treatment.

Quinine sulphate	10 grains.
Citric acid	30 "
Magnesium sulphate	30 "
Chloroform water	1 ounce.

This mixture is given 3 times a day 2½ hours after food for one week. The dose is then reduced to 1 ounce a day for further two weeks. Citric acid is converted in the gut into carbonate and this acts as an alkali.

After-treatment is an important consideration in malarial patients treated with cinchona alkaloids. At the end of a course the patient is anæmic and run-down and a combination of iron, arsenic and strychnine in small doses is often beneficial in building up the resistance of the patient and in the destruction of the remaining parasites not destroyed by quinine treatment. In some cases it has been found that quinine apparently produces little effect and the patients relapse. In such cases a dose of Novarsenobenzol, before quinine treatment, is helpful to overcome infection but this should be given with caution.

Provocative agents. Believing that the appearance of parasites in the blood in chronic cases of malaria renders them more liable to the action of quinine, certain substances have been used as activating agents to produce malarial relapses for securing the reappearance of asexual parasites in the peripheral blood. For this benzol in 0.1 to 0.5 mgm. doses has been given by the mouth in gelatine capsules or by injection. Subcutaneous or intramuscular injections of normal horse serum, milk, and strychnine nitrate 2 to 3 mgm. are used; application of X-Ray, ultra violet rays, cold douches, ice, etc., to the abdomen have been suggested. These methods are not very reliable and the

effects produced may not be immediate; several days may elapse before the parasites appear in the peripheral blood. Adrenalin, 1.0 mgm. (1 c.cm. of 1 in 1,000) subcutaneously, gives the highest percentage of positive results by producing a marked but temporary contraction of the spleen volume. Liquid extract of ergot 30 minims, 5 doses in all, orally, also thyroid extract and injection of pituitrin and salvarsan have been recommended; the last however is not without danger. Berberine sulphate in doses of 0.2 gm. sometimes acts well, 8 to 10 doses being given daily. Malaria may persist in latent form for years, the parasites lurking in the bone marrow and spleen.

Dosage. In non-malarious countries very small doses such as 2 or 3 grains are given. In tropical countries, the tendency is rather towards giving too large doses. It has been said that less than 20 grains of quinine in a day in an adult has no curative effect in malaria. This is not borne out by James' observations with induced malaria, who found that a few grains a day kept the patients suffering from induced benign tertian infections free from paroxysms for months. With such small doses however relapses occurred after long periods. Generally 20 to 30 grains by the mouth in 24 hours according to the weight of the individual, should be regarded as the maximum dose. Such doses always control malarial fever and when they do not, either the method of administration is at fault or the diagnosis is wrong.

A maximum dose of ten grains of the sulphate or hydrochloride by the mouth, three times a day for an adult, given for one week is quite sufficient to cure 70 per cent. of fresh malarial infections. In relapsing cases 5 to 7½ grains twice daily for one month in the case of malignant tertian infections and three months in the case of benign tertian and quartan infections are recommended by some. Doses larger than 20 to 30 grains daily lead to toxic symptoms, especially in weak individuals and are an absolute waste of the drug. The consensus of opinion at present is that a 7 to 10 days' course of treatment with 20 to 30 grains of quinine according to the weight of the patient is sufficient in all forms of malarial fevers. If there is a relapse, the whole course should be repeated.

The liver of rabbits is damaged by giving repeated intravenous injections of quinine, the cells of the parenchyma showing degeneration and fatty infiltration; the same may happen in man with large doses of quinine. Amounts larger than 30 grains a day are, therefore, by no means devoid of danger. Nierenstein (1920) stated that over 30 grains of quinine per diem is liable to injure the kidneys and cause albuminuria. It should not be forgotten however that acute and sub-acute parenchymatous nephritis occurs as an accompaniment of malaria and is readily benefited by quinine treatment. Massive doses also depress the cardio-vascular system and retard development of natural immunity on which the cure of the disease depends (McCarrison and Cornwall).

Quinine should not therefore be given in doses larger than 30 grains daily unless there is any special reason; even such small doses as 5 grains twice or three times a day given under rigid supervision are sufficient to cure an attack in persons weighing 100 pounds, but such small doses are not recommended for routine administration. It is preferable to give the larger doses already suggested, *i.e.*, 10 grains twice or three times a day.

Causes of failure of quinine therapy. If quinine is properly administered and absorbed it is bound to cure a large majority of the patients. The causes of failure may be:—(1) Adulteration of quinine. Quinine adulterated with lime, starch and other inert substances to the extent of 60 or 70 per cent. has not infrequently been met with in India; this is also the case with tablets. (2) Faulty preparation. Tablets may be prepared with unsuitable media and may have a coating quite impervious to water. (3) Non-absorption from the gastro-intestinal tract due to gastro-intestinal disturbances produced by the drug itself or complicating diseases such as ankylostomiasis, enteric, etc. (4) Low individual resistance. It is well known that some persons catch infection quickly and get rid of it with difficulty. (5) Use of insufficient doses. Hospital mixtures supposed to contain 10 grains to an ounce have been found to contain 1 to 2 grains in India. (6) Some of the patients may not be taking the quinine prescribed for them

owing to their dislike or prejudice against the drug, and they may be deceiving the physician. This can be immediately tested by taking 5 c.cm. of urine, boiling, and filtering the albumin if present and adding a few drops of Tanret Mayer reagent. A precipitate is formed if the alkaloid is being excreted in the urine. The drug should be given in hospitals by a responsible individual who sees that the mixture is swallowed. One or more of these factors may account for the failure of quinine to cure malaria. Intramuscular treatment may succeed in certain conditions when quinine by the mouth has failed for obvious reasons.

When quinine is being administered the physician should make sure:—

1. That quinine prescriptions are in full strength. There is evidence that mixtures in India are sometimes much below strength.

2. That the patient swallows and retains every dose prescribed and that he does not omit to take a single dose of the standard course given. Many causes may lead to omission, *e.g.*, vomiting may occur or the patient may wilfully reject a dose.

3. That the patient is absorbing quinine or any other alkaloids given. This may be ascertained by testing the urine.

Relapses. Relapses occur frequently in malaria. Administration of iodides, adrenalin, sera or vaccines, exposure to ultra-violet rays, excessive heat or cold, bring about a relapse and should be avoided. In spite of proper treatment with quinine many cases relapse. In addition to the selective action of quinine on the type of parasite involved, the chronicity or acuteness of the infection is an important factor. Sinton and Bird (1929) found that quinine cured 76 per cent. of primary infections, but in chronic cases it cured only 32 per cent., the balance all relapsed. Chronic benign tertian infections are more difficult to eradicate. These results were corroborated by treatment of induced benign tertian malaria for the cure of mental diseases, which was easily amenable to quinine; the relapse rate was only 1 to 3 per cent. with 30 grain daily doses for three days. The reason why primary infections of

benign tertian are more readily cured than chronic infections is not understood; some observers have stated that the parasites become more resistant.

So-called Quinine Fever. By this term is meant pyrexial phenomena without any or only a few malarial parasites occurring in patients taking small or medium doses of quinine. This is not produced by the alkaloid, as was supposed but is probably due to administration of insufficient quantities of quinine which are unable to control the infection. If the quantity of the drug is increased and adequate doses are given for 3 or 4 days at proper times, the fever disappears. Chopra and Das Gupta (1933) however observed a distinct increase in the parasites in the blood after intravenous injections of quinine in man and monkeys.

MODES OF ADMINISTRATION

Quinine may be given by the mouth, subcutaneously, intramuscularly, intravenously or per rectum. By all these methods it is absorbed into the circulation.

Oral administration. On account of the convenience of administration, the oral method is the one of choice. It may be given as a powder, in solution, in cachets or in the form of pills or tablets. When given in solution it is more readily absorbed than in any other form and therefore, this is usually employed. Tablets are more convenient and are less unpleasant than the solution, but they may not be absorbed. Even quinine in powder form is not recommended by many authorities. The usual mixture employed in hospitals is 5 to 10 grains of quinine sulphate, with 5 to 10 minims of dilute sulphuric acid in an ounce of water. Some prefer the bisulphate or hydrochloride, but these are more expensive. There is no evidence to show that the soluble salts are any more effective than the insoluble sulphates, though the absorption of the latter is somewhat slower. The powder and tablets take a longer time to absorb than the solution, but whether given in solution or in solid form, the alkaloid is absorbed into the circulation quite readily. The form of administration adopted should be such as to suit the individual patient. Uncoated tablets whether of the sulphate or of the

soluble salts, if fresh, are readily dissolved and are absorbed. If there is any doubt, they should be crushed and then administered. Some physicians prefer to give quinine in solution during the stage of active fever and to carry on with tablets during convalescence. The clinical condition of the patient is the best guide in deciding what method should be adopted. The condition of the tongue is an excellent indication of the state of the gastric mucosa. In ordinary attacks the tongue is moist and slightly furred, and under these circumstances the alkaloids are absorbed very well from the gut. If the tongue is dry, red and cracked, quinine is absorbed badly, and in such cases other means should be adopted. Quinine is generally absorbed readily from the gut; even in cases of malaria complicated with dysentery, quinine has been shown to be absorbed. If nausea and vomiting are present or in the bilious vomiting of malignant tertian infection, it is useless to give quinine by the mouth, as it cannot be retained. Vomiting in malaria has been attributed by some to hypo-adrenia, and it is said to be stopped by adrenalin in doses of 0.5 to 1 c.cm. of a 1 in 1,000 solution, by the mouth or by injection. Provided it is retained, quinine by the mouth is as efficacious as by injection, especially if it is given in the form of a solution, as regards its immediate effects on the fever, on the parasites and in the prevention of relapses. Experiments have shown that in solution it is absorbed with as great rapidity and appears in the urine almost as rapidly as when given intravenously. It is, therefore, the safest and the best method except when its effects on the alimentary canal are not desirable, or some other contra-indications are present.

The rapid absorption of the alkaloid and its quick disappearance from the blood, indicate the importance of ascertaining for each case, the time at which the drug should be administered, in order that it may destroy the vulnerable stages of the parasites. In clinical work James recommends that two facts should be remembered:—(1) sporulation begins about 2 hours before symptoms manifest themselves, (2) that the effect of a dose of quinine by the mouth begins within half an hour after its ingestion and lasts for more than six hours. He stresses the advantages of giving the drug 2 or

3 hours before the attack is expected. When more than one group of parasites are present, as in malignant tertian infections, sporulation occurs at irregular intervals and the plan of giving the drug at short intervals is the best. Others hold that quinine should be started when the schizonts are very young, as growth then ceases and degeneration ensues; if it is given when the schizonts are half grown, some are killed, some degenerate, while others carry on to sporulation. Quinine given during sporulation does not stop the paroxysms.

Experience shows that best results are obtained when these alkaloids are given 2 or 3 times daily in adequate doses. As the concentration of the alkaloid rapidly falls between 4 to 8 hours after ingestion it is considered advisable to administer the doses at intervals not longer than 6 hours.

The older writers recommended that quinine should not be given during fever, and even now this idea prevails in the mind of the public. There is no basis whatever for this belief. Even high fever is not a contra-indication for its administration. In malaria, quinine should be given regularly and continuously irrespective of temperature. Quinine has been shown to be just as effective in the febrile period as in the non-febrile period. It has also been said that quinine should not be prescribed with free organic acids as quinotoxin is formed, which is very poisonous. That is not true because quinotoxin is not a toxic substance.

Quinine tablets. There has been a great deal of controversy lately regarding the use of tablets. They have been condemned as 'brick bats', and some brands have been shown not to dissolve in weak acid solution even if kept in it for weeks. Alport (1919) thinks, quinine in tablet form is valueless and says it should never be used. Sugar-coating has been blamed for non-absorption of quinine. The fault really lies in the vehicle. Leger tried tablets of hydrochloride of quinine in 145 cases, testing the urine by Tanret Meyer solution. The alkaloid appeared in the urine in 2—2½ hours, was at its maximum in 5 to 10 hours and disappeared from the urine in 27 hours. All showed the presence of quinine, which indicated absorption when administered in this form. When using

tablets care should be taken that these are not too old and have not an impervious coating on them. If this precaution is taken, absorption is bound to take place.

Rectal administration. Quinine is much too irritating and in concentrated solutions may actually produce necrosis of the mucous membrane. This method is therefore not satisfactory and is rarely employed. Dysentery-like symptoms were produced with 30 grains of quinine in 2 to 4 ounces of water. The absorption of quinine by this route is uncertain and poor, and about three times the normal dose is required. The drug is seldom retained long on account of the pain and tenesmus which is produced. If diarrhoea or irritation of the bowel is present the solution is rejected. When it has to be given by this route it is advisable to give it in the strength of 10 to 15 grains in 4 to 5 ounces of warm normal saline mixed with 10 minims of tincture opii. The fluid is slowly injected with a rubber catheter. Fletcher (1924) has shown that absorption of quinine by the rectal route, as judged by testing the urine with Meyer's reagent, is poor, irregular and unreliable. He advises that it should not be given by this route if any other method is practicable.

By subcutaneous route. This method has been used though some physicians condemn it. Subcutaneous injections are painful and liable to produce necrosis; they are said to be followed by extensive and dangerous abscess formation and even tetanus. On the other hand it is said by some to be perfectly harmless and ensures rapid absorption of the drug. The manipulation is simple and can be safely entrusted to an assistant. In Russia subcutaneous injections of 0.5 to 1.0 gm. of quinine hydrochloride are given in all cases, in combination with anti-pyrin and iodine. Rarely, subcutaneous tumours have formed after injections of quinine.

Intracutaneous injections of 0.25 to 0.5 per cent. solutions of quinine hydrochloride have been suggested in the treatment of chronic malaria. Very small doses of quinine given by this method are said to be effective by anti-body formation.

By intramuscular route. This method of administering quinine is simple, but it should be carried out with strict aseptic

tic precautions and the skin should be thoroughly sterilised with tincture of iodine. The usual indications for administration by this route are blackwater fever, bilious remittent fever, persistent vomiting, drowsiness, or mental affections.

The syringe and the needles must be kept in absolute alcohol which is washed out with ether before the injection or they should be thoroughly boiled. It is advisable to use ampoules or sterules, but if these are not available the solution prepared for injection should be carefully sterilised. Bihydrochloride of quinine, preferably dissolved in distilled water, is employed and it should be thoroughly boiled. Sergeants advise that the strength of the solution should not exceed 3 per cent., but injections of dilutions as weak as 1 in 150 are known to have caused extensive necrosis of muscle and nerve tissue. If bihydrochloride of quinine is painful, solutions of urethane quinine or quinine and urea have been recommended. It is preferable to use dilute solutions, *i.e.*, $7\frac{1}{2}$ to 10 grains of the hydrochloride or bihydrochloride dissolved in 3 or 4 c.cm. of 0.85 per cent saline rather than in 1 to 2 c.cm., which is usually done. After injection the part should be massaged and collodion applied. The situations recommended for giving the injections are :—

(1) The gluteus maximus avoiding the line of the great sciatic nerve. This is the best situation, the spot selected being about 2 inches below the middle of the crest of the ileum. The needle should be introduced perpendicularly and if the point strikes the bone it should be withdrawn about a quarter of an inch and the quinine injected into the muscle. Care should be taken not to inject any into the subcutaneous tissue, as this will cause pain, stiffness and inflammation and very frequently an abscess.

(2) The cellular and muscular tissue below and external to the apex or angle of the scapula. The advantages of this site are that the injections are painless, there is no danger of damaging important nerves, the operation is not visible to the patient and the solution is readily absorbed.

(3) The vastus externus about its middle on the outer side of the thigh.

(4) The deltoid muscle avoiding the line of the musculospiral nerve. The best place is 2 inches below the acromion process.

The injections should not be given in the same place every day as this may produce necrosis and abscess. When the neighbourhood of a previously injected site is selected, inject in the circumference of a circle keeping at least half an inch away from the previous puncture mark. It is advisable to stop the injections and administer quinine by the oral route as soon as the paroxysms have been controlled.

Considerable differences of opinion prevail with regard to the advisability and efficacy of intramuscular injections of quinine. Some authorities maintain they should never be employed, while others consider them as invaluable in severe cases, especially the dangerous subtertian and also benign tertian infections which do not respond to oral administration.

According to Fletcher (1924), quinine given intramuscularly causes serious mutilation. The drug by this route is said not to be absorbed so quickly as when given by the mouth, nor is it more potent in preventing relapses. It produces immediate necrosis of the tissues into which it is injected; the dead muscle is usually not absorbed for a few weeks and may remain as a source of disease, forming an excellent nidus for the growth of bacteria from the blood stream. Cases of severe mutilation in the form of paralysis from injection near a nerve, or contraction of muscles from severe suppuration are frequently seen. Injection in the neighbourhood of a large nerve such as the sciatic, produces excruciating pain lasting for days; paralysis of muscles and contractures may occur. It is alleged that quinine given intramuscularly has certain advantages over the oral route and briefly stated these are:

(1) Its action is said to be more rapid and more vigorous. But it has been found that with intramuscular injections quinine appears in the urine (Meyer's test) on an average in 60 minutes, while if taken by the mouth in the form of a solution it appears in about 30 minutes. The action therefore cannot be more rapid.

(2) The effect of intramuscular injection is said to be more prolonged. It is believed in some quarters that quinine given by intramuscular route acts as a kind of reservoir and in this way a steady concentration of quinine is maintained in the blood. The origin for this belief is not known. It is found by actually testing the urine with Meyer's reagent that by whichever route it is given, quinine disappears from the urine in about 46 hours. Experiments on guinea-pigs show

that a large amount of quinine is absorbed after injection and only a small fraction of the total quantity injected can be found at the site of injection.

(3) It is said to have a greater power of preventing relapses. Rennie and Acton (1921) found in a malaria depot in the Himalayas (Dagshahi) that the percentage of relapses was the same whether the quinine was injected or given by the mouth.

(4) The therapeutic value of quinine given in this way is said to be greater. A number of medical men believe in the superior efficacy of intramuscular injections, on clinical grounds. Careful experiments have shown that there is little difference between the oral and intramuscular methods; if anything, the advantage is with the oral method. The reason for this belief probably is that by the oral route, administration of quinine has to be left to patients, who may or may not take the full dose of this unpleasant drug. Intramuscular injections are given by the physician himself and it is certain that a known quantity of quinine is introduced into the system. Besides it is not infrequently found that a mixture supposed to have ten grains of quinine has one or two grains only. The urine of patients taking quinine mixture should be frequently tested with Meyer's reagent to see if the alkaloid is present in the urine. This rough method is very useful.

The fact that necrosis of tissues is a constant accompaniment of intramuscular injections is not sufficiently appreciated by practitioners. Experiments by Acton and Chopra (1923) on rabbits and guinea-pigs showed that 24 hours after injection of bihydrochloride of quinine and other alkaloids (quinidine, cinchonine and cinchonidine) in the concentrations in which they are employed clinically, they produced very extensive oedema of the subcutaneous tissues and muscles round the site of injection; hyperæmia of vessels was very marked and hæmorrhages were present in the substance of the muscles. The bases of these alkaloids were found precipitated in the tissues, and muscles and fascia round the site of injection were friable and necrosed. In one case where the injection was given near the sciatic nerve the sheath showed signs of extensive damage. The damage to the tissues was marked on the 3rd day, but by the 6th day oedema and hæmorrhage had disappeared completely, while necrosis was still visible on the 10th day. Manson Bahr showed that continuous injections at the same site gave rise to patches of necrotic tissue about the size of an almond, but that there was no indication of pus formation. In weak, anæmic and debilitated subjects such dangers may exist. Fibrous tumours have occasionally been formed by irritation produced by quinine.

Cases of tetanus have occurred after quinine injections, but these are generally due to faulty technique. Semple considers that necrosis of muscle caused by injection of quinine forms a suitable nidus for the development of tetanus spores which are taken up by leucocytes from

the alimentary canal and deposited there. Recent work of Gye and Cramer on kataphylaxis has shown that such a possibility does exist. It has been shown that tetanus spores washed free of toxins and injected into an animal do not produce tetanus. If after some months in this animal, quinine is injected, tetanus develops at the site of injection of the alkaloid. This is due to the rupture of local defence mechanism. Quinine produces necrosis of tissues and this hinders the oxidation processes in the cells, the anaerobic conditions thus set up allow the spores to develop.

It will be seen, therefore, that intramuscular injections of quinine should not be given lightly or without most rigid attention to efficient aseptic precautions, not forgetting that tetanus spores are not killed even at 100°C . for a certain length of time. It is not justifiable to give quinine by this route in the treatment of ordinary cases of malarial fever when the patient can take the drug by the mouth. It should be reserved for severe cases of malignant tertian malaria with gastrointestinal symptoms, where quinine cannot be given by the mouth, or in young children and fat patients where intravenous injections cannot be given because the veins are difficult to find. It is true that hundreds of injections may be given without untoward effects, but the very next one may lead to disaster. Necrosis of the tissues is often a slow process and the results may not be apparent until weeks or months after the injections. Intramuscular injections do not produce cinchonism on account of the slow absorption of quinine.

Briefly stated, the dangers of intramuscular injections are (1) tetanus, (2) necrosis and formation of an aseptic abscess and (3) injury to nerves.

Intravenous method. The indications for intravenous administration of quinine are firstly, appearance of a very large number of parasites in the blood such as a dozen or more in a single field and secondly, pernicious malaria with nervous or mental symptoms such as drowsiness, aphasia and nervous twitchings.

Two methods for giving intravenous injection of quinine are recommended :—

(1) By giving it in 8 to 10 ounces (200-300 c.cm.) of saline. The apparatus for injection consists of a tall glass funnel one inch in

diameter capable of holding 8 to 10 ounces of saline. To this 3 feet of rubber tubing is attached and at the end of this a sharp needle is fitted, such as that used for salvarsan injection. A thermometer for taking the temperature is also required. For injection, 10 to 15 grains of quinine bihydrochloride are dissolved in 8 ounces of normal saline, the temperature of the fluid being 110°F. , to allow for cooling during its course through the apparatus. Large quantities of saline used for dissolving quinine may however produce dilatation of the right heart, especially if given too rapidly and collapse or even death may result. On the other hand, if the injection is too concentrated it may produce inhibition of the heart's action, directly or through the central nervous system. Extensive experience has proved that the use of more than 100 c.cm. of fluid for each case, as advised by some, is unnecessary and not devoid of danger.

(2) Injections may be given by means of a 10 to 20 c.cm. syringe, $7\frac{1}{2}$ to 10 grains or more of the salt being dissolved in 10 to 20 c.cm. of sterile warm normal saline. Some clinicians dissolve 15 grains of the bihydrochloride in 5 c.cm. of normal saline, heat it to boiling point and draw up into a syringe and inject. One of the superficial veins at the bend of the elbow is selected for the injection and a clean puncture should be made with a sharp needle. The fluid is slowly injected, the needle pointing towards the shoulder; several minutes are taken to complete the injection. The most rigid antiseptic precautions should be observed.

The intravenous route is especially recommended in serious and dangerous malarial infections, e.g., cerebral malaria, where we want the effect of the drug to be produced in a very short time and a few hours' delay would be fatal. One dose of 15 grains (1 gm.) is usually sufficient to stop the fever and to cause the disappearance of most of the parasites within 18 hours. The injection is repeated, if necessary, in 3 or 4 hours if by that time oral administration is not feasible. Many cases are lost owing to the hesitation on the part of practitioners in using this simple, quick and efficient method of controlling symptoms in grave cases. In chronic malaria when administration by the mouth fails to be effective, 4 or 6 intravenous injections may free the patient from parasites. It is important to give these injections so that they reach the heart in low concentration. Experiments on rabbits show that there is considerable difference in the minimal lethal dose of quinine, according as to whether it is given well diluted and slowly injected, or given

in concentrated form and injected rapidly. The minimum lethal dose by the latter method is much smaller.

The pulse should be carefully watched. If the injection is given too rapidly the pulse may become very feeble and alarming symptoms set in. Rigors sometimes appear within a few hours after injection; this is due to acidity of the salts, but it soon passes off. Some authorities advise the addition of a few drops of adrenalin solution to counteract the fall of blood pressure, but it seems to be unnecessary except in very severe cases of pernicious type. In some patients alarming symptoms appear in spite of all precautions. If the pulse becomes feeble give strophanthin or digitalin. If the injections are given slowly in a recumbent posture, the dangers of cardiac syncope are considerably reduced.

It has been demonstrated that large doses of ordinary quinine salts, *e.g.*, quinine hydrochloride, when given intravenously, are dangerous to life, the respiratory centre being more gravely affected than the cardiac centres. Acid hydrobromide in 15 grain (1 gm.) doses is less toxic to the respiratory centre than the acid hydrochloride and is preferred. Injections should be controlled by blood pressure observations especially in weak patients. It has been found, in experimental animals, that if intravenous injections are given continuously, circumscribed areas of necrosis appear in the adrenal cortex. Though the action of quinine injected direct into the blood stream is quicker than that of quinine given by the mouth or by the intramuscular method, it has no greater effect in destroying the gametocytes or eradicating the parasites from the body and so preventing relapses. Its action is more fleeting than when the drug is given by any other route, and for this reason, unless the administration of a dose is timed correctly in relation to the parasites, it is wise to supplement it as soon as possible by doses given orally. There is considerable evidence to show that quinine has little effect upon parasites contained in the red blood cells which are lying more or less stagnant in the small capillaries of the internal organs. It is chiefly effective against parasites which are free in the circulation, especially when carried to the peripheral parts of the body.

Acton and Knowles (1924) pointed out that the dangers of intravenous injections have been exaggerated. Phlebitis and thrombosis very rarely occur. Air embolism is a bogey; if proper care is taken $7\frac{1}{2}$ to 10 grains of acid hydrobromide in 15 to 20 c.cm. of sterile water is quite safe and can be conveniently given by a syringe. Larger quantities such as 15 grains in 5 c.cm. of saline (James) are not recommended as being too concentrated. It should be remembered that while the solubility of quinine hydrochloride is 1 in 35 of distilled water, it dissolves in 110 parts of Ringer's solution. About 90 per cent. of quinine injected disappears from the blood in a minute, and during that time it circulates in the blood in maximum concentration and has a destructive action on those parasites which have not reached the safe areas within the erythrocytes.

Cantlie and Mouharek (1924) in the Soudan treated a large number of cases of malaria by intravenous injections of quinine. They gave 9 grains of bihydrochloride, every day till the temperature became normal, as well as ten grain doses of bisulphate by the mouth. The injections occupied 30 to 45 seconds, the pulse was accelerated 5—17 beats per minute for not more than 3 minutes. Tingling in the mouth, ringing in the ears, sometimes constriction of the chest, rarely vomiting and on two occasions fainting occurred. Their observations showed that the action was more powerful and thereby the stay of the patient in hospital was cut short, but the relapse rate was 42.5 per cent. In another series of 1,103 cases there was a relapse rate of 77 per cent. after 6 to 8 injections in each case. A dose of 0.5 gm. of quinine given intravenously is as effective as 1.5 gm. by the mouth. If given on a fever-free day in benign tertian malaria, the paroxysm of the next day was cut short in 85 per cent. of cases against 64 per cent. with oral administration. Injections are also said to be effective in chronic malaria when administration by the mouth is not effective. Thrombosis of the vein often prevented the continued use of this method.

Intravenous injections of quinine should therefore be reserved for cases of special urgency such as cerebral malaria with delirium and coma, or malarial hyperpyrexia or malaria of pernicious type with persistent vomiting. They should be given

without hesitaton in such cases, and as soon as the condition of the patient allows it, oral administration should be started. Cordes (1928) treated 14 cases of cerebral malaria with $7\frac{1}{2}$ grains (0.5 gm.) of quinine in 10 c.cm. of water and saved all of them. In such cases puncture of the cisterna magna at the base of the brain and removal of 50 c.cm. of cerebro-spinal fluid is probably preferable to lumbar puncture. Cases with as many as 40 per cent. of the corpuscles parasitised, have been saved by injection of 15 grains of quinine daily for three days. Attention should be paid to the following points when giving intravenous injections :

(1) As they produce a fall of blood pressure and affect the respiratory centre, they must be given with the patient in the recumbent posture. (2) The injection must be a clean one into the lumen of the vein, otherwise it will produce necrosis and complications. If the needle misses the vein or slips out, stop the injection at once and before withdrawing the needle, suck back into the syringe all the solution that may have escaped into the tissues round the vein. (3) The injection must be given very slowly, at least 20 to 30 seconds being taken for the injection of each c.cm. (4) The solution should be freshly prepared.

The injections are followed by a transient feeling of dizziness lasting a few seconds while quinine can be tasted in the mouth before the injection is completed. It should be remembered that while intravenous quinine therapy is a useful addition in the treatment of critical attacks of malaria, it is useless in the prevention of critical attacks and in the prevention of relapses, and fails to rid the patient of parasites completely.

Intravenous administration of quinine should be given with caution when there is albuminuria, severe jaundice, organic disease of the heart, marked anæmia or debility and idiosyncrasy to the drug.

Summary. The best method of giving quinine is by the mouth and this is borne out by hæmatological as well as other evidence. It is best given in solution but owing to its very bitter taste vomiting may occur. Cachets are expensive but tablets if properly prepared are quickly absorbed after oral administration: they are convenient and cheap for routine treat-

ment, and for control of malaria on a large scale. Their therapeutic effects are not inferior. Subcutaneous injections find few advocates. Intramuscular injections should only be tried in those cases when the alimentary canal cannot tolerate quinine by the mouth. Under no circumstances should these latter be used for routine treatment of ordinary cases where quinine can be given by the oral route. Intravenous injections are preferable for severe and urgent cases, but as a routine treatment yield no better results than any other mode of administration. The physician treating the case will have to determine which is the best method to employ for the particular case.

As regards the time of administration of the alkaloid, we have already remarked that if quinine is given soon after a meal it hinders digestion by inhibiting the activity of the gastric and other ferments. It is advisable to give it $2\frac{1}{2}$ to 3 hours after a meal when the gastric contents are acid, the digestion has been completed and the stomach is nearly empty. If given at this time it rapidly mixes with the contents of the stomach and passes into the small intestine, from which it is rapidly absorbed into the circulation. There is also less liability of its producing irritation of the stomach which it undoubtedly does when given on an entirely empty stomach early in the morning or a long time after a meal. James prefers to give quinine 2 to 3 hours before the paroxysm of fever is due. Intramuscular injections may be given at any time, but it is preferable to give intravenous injections when the stomach is not loaded.

TREATMENT OF SPECIAL FORMS

Pernicious forms. The treatment of pernicious malaria should be started without a minute's delay. There are several types. In comatose or delirious forms the temperature may be normal or subnormal when the patient is first seen. In the bilious pernicious type vomiting is the chief symptom. In the intestinal form there is diarrhoea with bloody stools which on examination show malarial parasites in abundance. To save these patients, quinine in the form of the acid hydrobromide if possible, should be given at once by the intravenous route.

Cerebral malaria is the most fatal of all forms if immediate quinine treatment is not given. This condition is characterised either by sudden onset and rapid coma, or by hyperpyrexia, delirium, convulsions and other disturbances of the central nervous system. Early cases show symptoms of drowsiness, aphasia, nervous twitchings and a tendency to get out of bed. Alport (1919) recommended two intravenous injections of 15 to 20 grains during the first 12 hours combined with intramuscular injections of similar amounts in these cases. In semi-comatose, delirious and comatose cases he recommended even larger doses. It should however be remembered that large doses may damage the liver and the kidneys. The majority of cases met with in India can be controlled by giving one or two intravenous injections of 10 to 15 grains of quinine. In most of the critical cases one or two such intravenous injections given during the first 24 hours improve the condition of the patient and the temperature becomes normal. As soon as the patient is mentally clear an intramuscular injection may be given or quinine given by the mouth.

Chopra and his co-workers (1932) have shown that the first effect of intravenous injection of quinine often is to produce a definite increase in the number of parasites. When the infection is very heavy, *e.g.*, when over 50 per cent. of the corpuscles are infected no anti-malarial remedy, by whatever route it is given, appears to be of any avail. The same thing is observed in monkey malaria in which quinine almost always fails when the blood of *M. mulatta* is heavily parasitised.

Post-malarial nervous manifestations such as tremors, myoclonus, hemicrania, also improve under quinine treatment. Neuritis and choreaform movements may occur in malarial subjects and clear up rapidly under quinine. Disturbance of the glycogenic function of the liver has been recorded in acute malaria and glycosuria may be produced; asthma-like attacks may occur; both these conditions improve rapidly under quinine treatment.

In cerebral malaria in which there is accumulation of parasites in the brain, inhalations of amyl nitrite have been recommended. The object is to dilate the cutaneous vessels and to make the parasites more accessible to quinine. In abdominal

forms adrenalin is given in combination with quinine. This constricts the vessels of the skeletal muscles and dilates those of the splanchnic area.

Quinine in induced malaria. Artificial infection of man with malaria has recently been employed for treatment of neurosyphilis. Two methods are employed for transferring the disease to the patient. (1) By inoculation of the malarial blood either subcutaneously or intravenously. This method is not recommended as in spite of all precautions the blood may contain a mixed infection and cerebral malaria may follow with fatal results. Another danger is the possibility of transmitting syphilitic organisms from one case to another. The incubation period is 5 to 30 days, but if intravenous injections of infected blood are given it is shortened, being only 4 to 8 days. (2) By means of infected mosquitoes, *A. maculipennis* being generally used in England. *P. falciparum* will not however develop in this mosquito at low temperatures. The incubation period in benign tertian infection is 14 days; *A. bifurcatus* has also been employed. The virulence of the infection varies in different individuals from very mild infection to such a severe reaction that death may occur even from benign tertian infection, unless daily examinations of the blood are made and quinine treatment initiated at the proper time. Another less easily avoided danger is fatal rupture of the spleen; this has been recorded after artificially induced malaria in man. It has been shown that infection produced by direct inoculation of blood is very easy to cure permanently with small doses such as 3 to 10 grains of quinine, and relapses are very rare, being only about 2 to 4 per cent. On the other hand in cases infected through the mosquito bite, relapses with the same dosage occur in over 56 per cent. of cases. Even with 30 grain doses of quinine daily for five days, James (1925) found a relapse rate of 25 per cent. It would appear at first sight that the sporozoites injected by these insects are more resistant to quinine than the trophozoites of red corpuscles of man, but it should be remembered that the vitality of most of the individuals who contract malaria under natural conditions is lowered. Even in these natural infections the result of quinine treatment has

been much better than in the residual resistant cases who were invalidated from Salonika during the Great War. There may be a small percentage of cases with exceptional resistance to quinine, but among thousands of artificially produced benign tertian infections, 40 to 50 per cent. clear up spontaneously, and the great majority of the remainder yield readily to short courses of quinine. The treatment of the general run of malaria cases in warm endemic areas with quinine is therefore very satisfactory, and disparaging views of the value of quinine in malaria derived from some of the post-war experiences are not justified when applied to the action of the drug in malaria under normal circumstances. The importance of early and adequate treatment in malarial infections is clearly brought out from the successful treatment of artificially induced malaria. If this is done, the development of resistant cases is prevented. There are very few cases who will prove resistant to quinine. In induced malaria, quinine must be given at once if more than 25 parasites are found in a field. It is not easy to correlate the course of the temperature with the stage of growth of the parasites. James (1931) treated 300 cases, certified under the Lunacy Act, of which 20 per cent. were discharged cured. Malaria was not cut down by quinine but was allowed to smoulder on. No quinine was given or if at all, it was just enough to control infection. Very few of these patients were infective to *A. maculipennis*.

Chronic malaria. After the acute symptoms have subsided quinine treatment should be continued if such symptoms as enlargement of the spleen and anæmia are present. Quinine has no effect on the crescents directly, but the drug will kill the young trophozoites, young schizonts and merozoites thus preventing the formation of crescents. If anæmia is present it is better to combine quinine with iron and arsenic. Some prefer to give intravenous injections of salvarsan and allied compounds instead of arsenic by the mouth, but the former treatment should only be reserved for special cases. In malarial cachexia small doses of quinine, combined with iron, arsenic and strychnine are the best.

Malaria complicated with pregnancy. Owing to the oxytocic properties of quinine, opinions have differed regarding its administration in pregnant women. It is now generally agreed that in malaria occurring in pregnancy, quinine must be administered and that the disease itself is far more likely to produce abortion than is quinine. Benign tertian malaria causes little trouble; but the malignant tertian infection is very liable to produce abortion, hæmorrhage and death. Quinine does not act as an oxytocic in malaria in pregnancy, provided labour has not already commenced. In some cases quinine can and does strengthen the normal uterine contractions of pregnancy, causing perceptible pains where labour has not commenced. On the other hand quinine has been administered to many pregnant women, sometimes in fairly large doses, without causing untoward symptoms and pregnant women have taken quinine prophylactically for long periods, without showing any tendency to abort, provided they keep free from malaria. Cases have been known where the prompt administration of quinine has quietened the pains which had already commenced and abortion was threatened. Kadaner (1928) in the Congo found 0.3 to 0.5 gm. of quinine daily essential for the prevention of abortion in patients suffering from malaria. The blockage of the placental circulation by sporulating masses of the parasites may itself lead to the death of the foetus and its expulsion. Congenital infection has been recorded by many observers and parasites have been actually found in the blood of an infant before the placenta is expelled, indicating transplacental infection. Infants frequently die of malaria within a few days of their birth in areas with a high malarial infection rate, and administration of quinine to the mother before delivery may avert this danger. In malarial subjects quinine should be given after child-birth to prevent the attack of fever which always follows parturition. Quinine at this stage is also further beneficial in increasing uterine contractions and thus aiding involution.

In pregnant women it is advisable to give smaller and divided doses of quinine more frequently rather than large doses less frequently. With large initial doses abortion may be

threatened but may not take place. Twenty grains intravenously have caused miscarriage in a case in four hours. Smaller doses such as 4 or 5 grains should therefore be given by the mouth every 4 hours until the patient receives 16 to 20 grains in 24 hours. This procedure decreases any chance of abortion in malarial fever. The preliminary purgative should not be omitted though in pregnancy it must necessarily be mild. A little bromide of potassium or opium may be combined with quinine, if necessary. In debilitated and anæmic individuals quinine acts more powerfully on the uterus, and in these persons greater care is required and smaller doses are to be preferred. The patients should lie in bed when the drug is being administered. In a large number of cases recorded, no ill-effects seem to have been produced even with such big doses as 30 grains in a day. Quinine given hypodermically is said to be more liable to produce abortion.

Quinine in children. Children tolerate quinine well and relatively larger doses may be given than are indicated by the age of the patient. The drug should be administered as soon as the diagnosis is made. In babies, it is advisable to give euquinine (quinine-ethyl-carbonate) or aristochin which is a tasteless powder. For a baby one year old, $1\frac{1}{2}$ grain every six hours should be given. For children of 3 to 5 years 5 grains of euquinine every six hours; for 5 to 10 years 7 grains of euquinine or 5 grains of sulphate or bishydrochloride may be given. In children under 10 years it is better not to give more than 5 grains of quinine in a single dose. The administration in children should be closely controlled by microscopic examination of the blood for parasites, when these disappear smaller doses should be given.

OTHER CINCHONA ALKALOIDS IN MALARIA

Quinine till quite recently has been employed in the treatment of all forms of malaria, but Acton has shown that while it cures 90 per cent. of malignant tertian infections if properly given, in the benign tertian infections the primary cures were not more than 18 to 30 per cent. even after a two months' course.

Cinchona febrifuge which contains all the alkaloids of cinchona bark gave a cure rate of about 50 per cent. so that it can be reasonably concluded that there must be alkaloids other than quinine, which are responsible for this enhanced rate of cures. These other alkaloids were tested individually. Cinchonine and quinidine in ten grain doses twice daily showed a cure rate of 60 per cent. of benign tertian infections after a short course of three weeks; these alkaloids were therefore preferred by him in these cases.

Fletcher recently tested the action of different cinchona alkaloids individually in the treatment of malaria; his conclusions are as follows:—

(1) In doses of 10 grains twice a day the 4 alkaloids, *i.e.*, quinine, quinidine, cinchonine and cinchonidine appear to be of equal value in bringing about the disappearance of malarial parasites in patients weighing 100 pounds.

(2) None of these alkaloids produce toxic symptoms when given in this quantity, not even cinchonine and quinidine.

(3) In doses of 5 grains twice daily, cinchonine does not appear to be quite so potent as quinine and quinidine.

(4) Cinchonidine sulphate is definitely inferior to other crystallisable alkaloids, when given in small doses.

(5) Quinidine sulphate acts better on the quartan parasites than quinine.

(6) Quinidine in 5 grain doses does not cause the disappearance of the parasites; in 10 grain doses it cannot be tolerated as it produces severe nausea, vomiting and collapse.

It would appear from this that there is little to choose between the different crystalline alkaloids of cinchona bark so far as their action on benign and malignant tertian parasites are concerned. Fletcher's conclusions regarding the toxicity of quinidine are not borne out by our experience. It is liable to produce depression of the heart, and fainting and sudden deaths have been known to occur, especially in those suffering from emaciating diseases such as kala-azar.

Dale and James (1925) found the curative effects of quinine, quinidine and cinchonine the same on all forms of malaria, and except for the depression caused by the last, there was no difference in toxicity. Ciuca (1925) made similar comparative tests with quinetum which is a form of cinchona febrifuge containing all the alkaloids but only 15 per cent. of quinine and 5 per cent. of quinidine. He found it to be as effective as pure quinine hydrochloride. In bird malaria the results with cinchonine, cinchonidine and quinidine ran closely parallel with those obtained in man. The Sergeants and Catnei (1925) found cinchonine and cinchonidine effective in removing malarial parasites from the blood and in reducing the size of the hypertrophied spleen; they found cinchonidine more powerful than cinchonine in splenomegaly. The Malaria Commission of the League of Nations (1927) stated that in doses of 1.0 gm. daily, quinine, quinidine and quinetum are equally efficient in producing a clinical cure in malaria. Cinchonidine in doses of 1.5 gm. equals the efficacy of other alkaloids.

It is evident from the above that much waste has resulted in using only pure quinine, and cheaper and equally efficacious alkaloids might well be substituted in the treatment of ordinary cases of malaria while the more expensive and refined alkaloids may be reserved for severe types of cases.

Quinidine. The data at present available are not sufficient to justify a definite pronouncement whether quinidine is in all respects an efficient and quite satisfactory substitute for quinine against malaria. It has been considered by some to be as prompt in its action against benign and malignant tertian as quinine and as well borne, while others did not consider it quite equal to quinine especially as regards preventing relapses; it was prone to cause more nausea. Fletcher (1925) considered quinidine as good as or even slightly better than quinine bisulphate in its effects. Sinton (1930) however thinks that quinidine has no more marked effect in producing a permanent cure in benign tertian malaria than has quinine. Quinidine is more expensive than quinine and has a more toxic action on the heart and this limits its use. Before prescribing it the heart should be carefully examined and the drug should be given in doses not bigger than 5 grains three times a day with citric acid. Fletcher found that in doses of 0.1 grain per

kilo. of body weight twice daily, it removed parasites from the peripheral blood as rapidly as similar doses of quinine.

Cinchonidine. Cinchonidine sulphate is the least toxic of all the cinchona alkaloids. Investigations of Fletcher and others have shown that in 10 grain doses twice daily, it is almost as effective against malaria as quinine and on account of its lower toxicity it is well borne.

Cinchonine. MacGilchrist (1916) and Silvestri (1921) considered cinchonine to be as effective against malaria as quinine; Acton (1920) thought it was the most toxic of all the cinchona alkaloids. Fletcher (1925) investigated its effect on behalf of the Medical Research Council and came to the following conclusions:—

(1) Cinchonine in doses of 0.1 grain per kilo. body weight is less efficacious than quinine in reducing fever, and in clearing malaria parasites from the peripheral blood.

(2) Cinchonine in doses of 0.1 grain per pound weight of body is as effective as quinine.

(3) Cinchonine is not more toxic than quinine.

Rogers (1917), Cuica and others (1925) found that cinchonine was slightly less efficient in removing the schizonts of benign tertian infection from the blood, and much less efficient in dealing with gametocytes.

Rogers (1918) recommended cinchonine bihydrochloride for intramuscular injections because it is more soluble than the corresponding quinine salts and therefore more rapidly absorbed. It is said to produce less injury to the muscle, is less painful, gives rise to less induration and is as effective as quinine against malaria. Because cinchonism is quickly produced by injection of this alkaloid it was thought that it was more rapidly absorbed than quinine which does not produce these symptoms so readily. He advised 10 to 15 grains daily in 1½ to 2 c.cm. of saline in the deltoid for four consecutive days, after which quinine is given by the mouth. Experiments by Acton and Chopra (1923) showed that there is no marked difference in the absorption of quinine and cinchonine after intramuscular injection and the damage to the tissues is about the same. The production of symptoms of cinchonism after its injection is due to the greater toxicity of the drug and not to its rapid absorption.

Quinoidine. This name has been given to the combined amorphous alkaloids which remain after all the crystallisable alkaloids have been

removed from an extract of cinchona bark. Opinions vary regarding their effectiveness against malaria. Prain (1902) and Waters (1916) found it to be as effective as quinine ; Acton (1920) and Fletcher (1923) showed that it has no appreciable effect against malarial parasite in 5 grain doses twice daily. In 10 grain doses, three times daily, it was effective, but produced toxic symptoms, such as vomiting and diarrhoea. It is possible that the drug used by the two classes of workers was different or possibly the method of preparation now used renders the non-crystallisable residue less efficient. In any case, the results obtained do not seem sufficiently valuable in malaria to counteract the drawbacks of its toxicity.

From a perusal of the foregoing section, it will be seen that a good deal of confusion exists with regard to the cinchona alkaloids. The Commission of the League of Nations assisted by an expert Committee investigated the matter and came to the following conclusions (1932) :—

(a) The name 'quinetum' should be reserved for a preparation consisting of quinine, cinchonidine and cinchonine in equal parts. If this preparation were made by extracting those alkaloids from the bark of *Cinchona succirubra* (which usually contains them in approximately equal quantities), only a small addition of one or other of the crystallisable alkaloids would be necessary in order to equalise the amount of each alkaloid in the preparation.

(b) Instead of continuing to use the name 'cinchona febrifuge' which in the past has been applied to alkaloidal mixtures of very different composition, it is suggested that a new standardised preparation containing all the alkaloids in cinchona bark should be recommended for general use in treating malarial populations, and that its name should replace the name 'cinchona febrifuge'. The new preparation should be standardised to contain not less than 70 per cent. of crystalline alkaloids, of which not less than 15 per cent. must be quinine. The amount of amorphous alkaloids must not exceed 20 per cent., mineral matter not more than 5 per cent. and water not more than 5 per cent. The name suggested for this new pre-

paration is 'totaquina.' The compositions (approximately) of available samples of the two types of Totaquina are as follows :—

		Type I, made by extracting the total alkaloids from cinchona bark	Type II, made by add- ing sufficient alkaloids to the residues of quinine manufacture.
		<i>C. succirubra.</i>	<i>C. robusta.</i>
	Per cent	Per cent.	Per cent.
Quinine	25.28	28.46	14.79
Cinchonine	27.67	16.00	55.11
Cinchonidine	84.18	47.58	7.10
Quinidine			6.21
Total crystallisable alkaloids	87.08	92.0	88.21
Amorphous alkaloids	8.86	8.70	10.47
Moisture	0.99	1.00	1.77
Ash	0.68	1.67	2.18

It will be seen that, while the alkaloids in Type I are chiefly quinine and cinchonidine, the chief alkaloid in Type II is cinchonine. Also Type II contains quinidine, which is not present in Type I and it contains a larger amount of amorphous alkaloids.

On account of their different alkaloidal contents, the therapeutic properties of Types I and II must be considered separately.

Results of tests on bird malaria. Professor Giemsa has made toxicity and therapeutic tests of samples of each type in comparison with quinine and hydroquinine by the method of Roehl. The results showed that all the samples tested (three of Type I, one of Type II) were a little more toxic when injected intravenously into rabbits than hydrochloride of quinine administered in the same doses, and that, as regards their therapeutic action on the parasites of bird malaria (*P. relictum*), all of them were inferior to quinine. The sample which contained the largest amount of quinine (a preparation of Type I containing the total alkaloids of *C. robusta*) was the most active therapeutically, and of the two samples of Type I the preparation containing the total alkaloids of *C. succirubra* came next. The sample of Type II made from the residues of quinine manufacture and which contained less quinine but more cinchonine than any of the others was found to be least effective

therapeutically. Professor Giemsa concluded that the therapeutic action of the preparations was directly proportional to the amount of quinine which they contained.

Results of tests on human malaria. Tests on benign tertian malaria, *P. vivax*, intentionally induced by the bites of mosquitoes on ten individuals, were carried out at Horton under the direction of the Malaria Commission. Both types of totaquina were used. The composition of the samples tested is given below :—

	Type I (total alkaloids of <i>C. succirubra</i> .)	Type II (quinine residues.)
Quinine	38.4	15.8
Cinchonine	21.7	55.4
Cinchonidine	34.7	5.7
Quinidine	0.0	5.2
Amorphous alkaloids ...	5.8	18.4
Moisture	0.76	1.9
Ash	0.6	2.1
Total crystallisable alkaloids ...	94.8	81.6

The results are very much the same as those obtained by Professor Giemsa in tests on bird malaria. They may be summarized as follows:—

(1) One dose of 5 grains (0.3 gm.) of totaquina of either type has practically no effect on the fever or parasites. It is necessary therefore to use a single dose of 10 grains (0.6 gm.) for the test.

(2) A single dose of 10 grains of totaquina Type I produces the same effect in aborting the fever and in reducing the parasites as is produced by a single dose of 5 grains of quinine.

(3) A single dose of 10 grains of totaquina Type II has practically no effect in aborting the fever or in reducing the parasites. With this type of totaquina it is necessary to use a single dose of 20 grains (1.2 gm.) to produce the same effect as is produced by a single dose of 5 grains of quinine.

It appears from these results that totaquina Type I (total alkaloids of *C. succirubra* or *C. robusta*) when used in ordinary clinical therapeutic doses for curative purposes—*e.g.*, 1.2 gm.

(20 grains) daily for five to seven days—should give about the same good result as is given by quinine in the same doses. If this is so, and if this type of totaquina can be obtained more cheaply than quinine, it would be advantageous to use it for general purposes instead of the single alkaloid.

Cinchona febrifuge, it has been pointed out, is a mixture of all the cinchona alkaloids of the *C. succirubra* bark. Residual alkaloids are a mixture of the alkaloids precipitated from the mother liquor after most of the quinine in the bark of *C. ledgeriana* has been extracted. To this latter certain proportions of quinine sulphate are added and the mixture is used as a substitute for quinine. Both these products are cheaper than quinine and under the name of cinchona febrifuge have been used in the treatment of malaria in India with gratifying results. The following mixture is prescribed:—

Cinchona febrifuge	10 grains.
Citric acid	20 „
Magnesium sulphate	30 „
Peppermint water	1 ounce.

One ounce of this mixture is prescribed three times a day 2½ hours after meals, for one week. It has been found quite effective, but it is liable to produce nausea and vomiting, as the amorphous alkaloids present stick to the mouth. The majority of patients, however, tolerate it well if it is taken at the right time, *i.e.*, 2½ hours after food. If nausea and vomiting occur a dose of 15 minims of 1 in 1,000 adrenalin or a minim of tincture of iodine in a little water, before the cinchona febrifuge mixture is given, will check the vomiting. If necessary, 5 to 10 minims of tincture of opium may be given. Fletcher (1925) came to the conclusion that cinchona febrifuge with 7 to 10 per cent. of quinine is as efficient as quinine therapeutically in doses of 10 grains twice a day and it is no more toxic.

Derivatives of quinine and cupreine in malaria. Henry and Brown (1923) showed that the toxicity of quinine base is greater to the paramoecium than that of its salts. Quinine base is also effective in clearing the blood of malarial parasites in human patients. Insoluble salts of quinine such as quinine tannate, though tasteless, are not very effective against malaria. Equisinine (quinine-ethyl carbonate) is taste-

less and bulky, and it is effective in removing the parasites from the peripheral blood, as it is readily hydrolysed in the body to quinine itself. The hydroalkaloids such as hydroquinine hydrochloride, etc., are said by some to be more effective than quinine, by others less so. Cupreine sulphate in doses of 1 gm. was found by Giemsa and Werver (1914) to be a good substitute for quinine in human malaria, but it is expensive and toxic. These observers also obtained good results with quinethyline and quinpropyline, in doses of 0.3 to 0.4 gm. in human malaria and with these compounds and quinamyline in bird malaria. Ethylhydrocupreine or optochin has been tried in malaria with disappointing results.

CHAPTER XX

TOXIC EFFECTS

Quinine is one of the least toxic of the alkaloids, the lethal dose by the mouth in animals being 1.0 gm. per kilo. body weight. Frogs are killed by 1 mgm. per gramme by the mouth and by about half this amount given by injection. Pigeons are not killed by 3 gm. per kilo. by mouth although 0.5 gm. is fatal when given intramuscularly; rabbits are killed by 1.0 to 1.5 gm. by mouth, by 0.25 to 0.5 gm. subcutaneously and by 0.07 gm. intravenously. A dose given into the artery of a limb does not kill but causes complete paralysis of the part supplied by the artery. It is suggested that this action is due to paralysis of the leucocytes which plug the vessels of the limb, causing palsy. The fatal dose in man is 8 to 15 gm. by the mouth but in a few instances as much as 30 gm. has been taken without producing death. Two to three grammes can be tolerated but 5 gm. always produces toxic effects.

Toxic effects produced by cinchona alkaloids. There has been a tendency on the part of some clinicians to give large doses of quinine in the treatment of malaria. It should be remembered that the amount of this drug required to produce toxic effects varies enormously in different individuals. The solubility of the salt of the alkaloid employed, the vehicle in which the drug is given, the route of administration, the total quantity retained in the system, and the individual sensitiveness or idiosyncrasy of the patient to the drug, are some of the factors which play a part in all cases. In the majority of patients serious symptoms follow the administration of a total dose of 40 to 80 grains, while much smaller doses have produced toxic effects in sensitive individuals. Repetition of doses of quinine in patients who have suffered from cinchonism is not desirable.

The toxic effects produced by quinine can be discussed under the following headings:—

Quinine idiosyncrasy. Some individuals show very peculiar susceptibilities in regard to quinine, even when such minute quantities as 1/16 grain are given. The symptoms which manifest themselves are a variety of skin eruptions such as scarlatina-like erythema, urticarial rashes, intolerable itching or bullous eruptions, which may be accompanied by fever. Other symptoms are dyspnoea, fever, nausea and vomiting. Sometimes there are giddiness and fainting. There may be extravasation of blood in the skin and perhaps in the intestines and kidneys; occasionally there is severe prostration which disappears by the following day, but reappears some weeks later when the dose is repeated. In some cases itching of the skin and vesicular eruptions are produced by contact with quinine solutions. Sometimes cinchonine or quinidine does not produce idiosyncrasy in cases in which quinine does so, and so either may be substituted. Idiosyncrasy may suddenly appear in persons who formerly have taken large doses of quinine without any disagreeable consequences. It may also declare itself by occurrence of toxic symptoms after small doses (deafness, amblyopia, etc.) which are usually produced after large doses. This idiosyncrasy is not commonly met with in the tropics, where large doses such as 20 to 45 grains are given in 24 hours and it appears to be similar to that of potassium iodide in which idiosyncrasy is more commonly seen with small doses than with large ones. If the serum of a person suffering from idiosyncrasy to quinine is injected intraperitoneally into a guinea-pig, the animal's susceptibility to quinine is greatly increased. Rarely, quinine produces a paradoxical or contrary action, producing an enormous rise of temperature accompanied by rigors instead of the expected fall. This phenomenon still remains unexplained.

In susceptible individuals local application of quinine solution (1 in 10 to 1 in 1000) to the scarified skin produces a marked reaction which is not given by normal individuals. This may be used as a harmless test for quinine idiosyncrasy. The skin reactivity may be met with in the case of some laevorotatory alkaloids, *e.g.*, cinchonidine, ethylhydrocupreine, etc., and more rarely in dextrorotatory isomers such as quinidine, cinchonine,

ethyl-hydrocupreidine. Sensitiveness to quinine is not congenital and does not exist in blood relations.

Desensitization. This has been proposed and tried successfully in some cases. The patient is given 5 mgm. of quinine bisulphate plus 0.5 gm. of sodium bicarbonate to start with, by the mouth. After 1½ hour 0.5 gm. of sodium bicarbonate and 0.1 gm. of quinine are given. The two doses of quinine are repeated daily, the desensitising dose being left at 5 mgm. and the second dose being increased by 0.1 gm. every day. Another plan is to give 0.5 to 1.0 c.cm. of adrenalin by injection, followed 20 minutes later by a small dose of quinine such as 0.05 gm. Next day the same injection of adrenalin is given, but the dose of quinine is increased.

Cinchonism. This name is given to the early symptoms, chiefly connected with the central nervous system, which appear when quinine or other cinchona alkaloids are given in large doses. This should be differentiated from idiosyncrasy which is a condition of increased susceptibility and which is brought on by very small doses. Some individuals, however, are much more liable to get cinchonism than others. The power of producing cinchonism varies with the different alkaloids, cinchonine being the most powerful, next comes quinine, then quinidine and lastly cinchonidine. The association between the symptoms of intoxication and high concentrations of the alkaloid circulating in blood is very striking. These early symptoms are nausea, vomiting, headache (due to cerebral congestion), ringing in ears, giddiness and disturbed vision (due to selective changes in the vessels of the eye and ear). Minor symptoms may be somewhat diminished by bromide salts.

When a toxic dose of quinine is taken, the first symptom is usually severe bursting headache, accompanied by loud roaring in the ears and deafness, which may be complete but is rarely permanent. There is loss of taste and smell, mental depression, photophobia, and later blindness, at first partial and then complete. With very large doses abdominal pains with nausea, diarrhoea, vomiting and general muscular weakness occur followed by difficulty of speech, confusion of ideas, somnolence, loss of consciousness, delirium, general paralysis, coma, at times

convulsions, and finally death from collapse. Chills and cold sweats are also common, the pulse is rapid and weak and the respirations shallow. Large doses paralyse first the brain and respiratory centre and later the heart. The medullary centres as a rule are not affected till very late, and patients may recover even after very large doses. Quinine amblyopia and amaurosis have already been referred to. Quinine also produces skin rashes. There may be erythema, urticarial weals, swelling of the tongue and face, œdema of the eyelids, a scaly condition of the skin and a generalised itching eruption. It may also cause hæmorrhage from the nose, uterus and kidneys.

Quinine albuminuria. A fact of great clinical interest is that when large quantities of quinine are passed through the kidneys, temporary albuminuria is produced. Ramsden found that the proportions of quinine excreted diminished when the dose of the drug exceeded 2 gm. by the mouth, and Nierenstein found that such a dose given orally or 1.2 gm. given intramuscularly, frequently produced albuminuria. The kidneys can excrete very large quantities of quinine and as much as 2.2 gm. have been recovered from the urine within a day. Quinine is usually excreted at a concentration of 600 mgm. per litre in the urine which is about sixty times its concentration in the blood. Repeated administration of quinine does not increase the power of the body to destroy the drug, for the same proportion is excreted after prolonged administration. According to Marchaux 9.75 per cent. of cases taking quinine have albumin in the urine. The dosage, mode of administration (intramuscular injections are more liable to produce it), diet, climate, etc., are all factors concerned. Sinton and Lal (1927) found that the incidence of albuminuria was much less when quinine treatment was combined with alkali than when quinine was given alone.

Apart from albuminuria produced by quinine, renal changes occur in malaria. From ancient times quartan fevers have been recognised to be the cause of nephritis. Giglioli (1932) has drawn attention to cases of sub-acute and chronic Bright's disease where symptoms develop with the appearance of the parasites in the blood and disappear on the administration of quinine.

Visceral degeneration. Cornwall (1920) showed degenerative changes in the suprarenals and the kidneys, and increased degeneration of the erythrocytes in the spleen after large doses of quinine in rabbits. That quinine has toxic effects on the liver has been experimentally proved. Intravenous injections of moderate doses in rabbits produce progressive degeneration of liver cells, which increases with the increase of dosage. Quinine has a certain amount of hæmolytic effect on the blood cells especially in high concentration. It modifies the response to other hæmolytic agents such as acid solutions.

Macht and Teagarden (1923) showed that quinine and quinidine are more toxic to rats exposed to sunlight or to a quartz lamp than to those kept in the dark. Exposure of quinine solution to ultra-violet light produces chemical changes which render it more toxic to paramœcia *in vitro* and also more effective in bird malaria (1920).

The toxic effects of the other cinchona alkaloids are similar to those produced by quinine, but they show important differences that might make them therapeutically less desirable. Cinchonine and cinchonidine in large doses produce tonic and clonic convulsions, the site of their action on the brain being located below the optic thalami. Quinidine has a stronger depressant and paralysing effect on the heart. Cupreine is about half as toxic as quinine. Cinchonine is more toxic than quinine and produces salivation, hallucination and epileptiform convulsions. It has little effect on the blood pressure.

The grave effects of cinchonism are only met with when the dose of quinine is increased beyond 40 to 60 grains a day. Such large doses were prescribed at one time by practitioners in India and were often continued for long periods. These undoubtedly do harm. As a rule a maximum dose of 20-30 grains per day, according to the weight of the patient, divided into 3 or 4 doses, are quite sufficient in an adult to control the fever. Such doses are quite safe and effective and as a rule cause no untoward symptoms. There is no particular point in giving very big doses by the mouth as the intravenous and intramuscular method can always be resorted to when there is doubt regarding its absorption from the gut.

A form of toxæmia occurs in patients taking large doses of quinine for prolonged periods. In the old days patients who had suffered from malarial fever were put on large doses of quinine for periods ranging from 1 to 3 months, and this condition was not infrequently met with. The patients looked pale and anæmic, they were listless, had no inclination to make any exertion and had lost their appetite for food. There was generally a jaundiced tinge about the conjunctiva and the temperature was usually subnormal. All these symptoms were put down as after-effects of malaria, but they were due to the action of quinine on the gastro-intestinal tract and other organs, because stoppage of the drug or decrease in the dose rapidly improved the condition. The toxic effects of quinine have been attributed by some to the formation of a body called quinotoxin which is formed by the action of free organic acids on quinine, and it is suggested that such conditions arise in the gut. It is however found that this substance has a very low toxicity and could not be responsible for these effects.

Treatment of cinchonism. Numerous drugs have been tried to obviate cinchonism, and of these caffeine given subcutaneously or intravenously shortly before the administration of quinine is the best. To relieve headache phenacetin has been tried but it may depress the heart. If nausea is present 20 to 30 grains of sodium bicarbonate in a tumblerful of hot water is useful. Bromide of quinine is said to produce fewer symptoms of cinchonism, and therefore quinine has often been prescribed with hydrobromic acid.

CHAPTER XXI

MODE OF ACTION IN MALARIA

Rationale of action of Cinchona alkaloids in malaria. The cinchona alkaloids have a remarkable action against malaria. They kill the parasites responsible for the disease without injury to the host. Before the parasites were discovered the action of quinine was ascribed to some influence on the nervous system. Many years ago Binz, from his experiments with quinine and protozoa, prophesied the discovery of an organism belonging to this order as being the cause of malarial fever. This prophecy was fulfilled when Laveran in 1880 discovered the plasmodium in the blood of patients. If blood containing parasites is examined on the warm stage of a microscope, in the presence of minute quantities of quinine, movements of the parasites are arrested; if however the drug is given by the mouth, three hours elapse before the endocorpuscular forms become immobile, granular and lose their affinities for certain stains. It has been found that quinine does not attack the parasite with equal virulence in all the stages of development. The asexual forms as a rule are much more vulnerable; the sexual forms of *P. falciparum* appears to be hardly touched. The action of cinchona alkaloids controlling attacks of malarial fever is not understood. There are many points in connection with directing the attack of these alkaloids upon the most vulnerable stage of the parasite, about which we have not sufficient knowledge. With regard to the parasite we should know in what part of the body sporulation occurs and how long before the fever it occurs and how long it lasts. Does it occur in positions where quinine can easily penetrate? How soon after administration by different methods will the alkaloids be present in the system where they are required, when will they produce their maximum effects and how long will they remain there? Some of these points are discussed below.

The concentrations of quinine in the blood attained after therapeutic doses are not sufficient to kill the malarial parasites by their direct action. Other factors therefore must come into play.

Ramsden, Lipkin and Whitley (1918) found that quinine was present in the blood in a strength of 1 in 100,000, seven hours after administration. In a number of human cases treated with intravenous injections no direct correlation was found to exist between the concentration of quinine in the blood and the disappearance of the parasites. From the blood, a certain amount, varying with the individual, but averaging about 40 per cent. of the total amount administered,

is eliminated by the kidneys within three to twenty-four hours. Very little passes out in the faeces unless there is diarrhoea. The balance is fixed in the tissues, more in some than in others. For example the adrenals fix a larger quantity in proportion to their weight than do the liver, spleen, kidneys or bone-marrow. It is apparent from these studies that quinine makes only a brief stay in the blood circulation, and is only present here in minute traces; the blood corpuscles taking up very little. Acton and King (1921) concluded that the distribution of quinine between plasma and corpuscles was about equal. The question is of some importance as the malarial parasites being intra-corpuscular, no drug should be used as a chemotherapeutic agent unless it readily penetrates the red cells.

The following concentrations of quinine were found in the blood by Acton and King after 15 grains were given on an empty stomach.

Quinine

Interval after administration. (hours.)		Concentration of quinine in blood	Amount in blood (mgm.)	Per cent. of the dose taken.
1	...	1 in 150,000	33	3.3
2	...	1 in 187,000	27	2.7
3	...	1 in 225,000	22	2.2

Hydroquinine

1	...	1 in 250,000	20	2.0
2	...	1 in 280,000	18	1.8

Morgenroth (1918) estimated the dilution of quinine as greater than 1 : 150,000. Hatcher and Gould (1927) could not detect the drug in a single specimen of blood taken from 12 patients (after an interval of 30 minutes in 7 cases and up to 2 days in others) after 14.5 gm. of the drug was given orally and intramuscularly. After intravenous injection, a concentration as great as 1 : 20,000 may be obtained but rapid elimination from the blood stream takes place. It is extremely difficult to bring the concentration in the blood up to 10 mgm. per litre, the highest figure, so far obtained experimentally being 16.6 mgm. which was associated with very severe symptoms of poisoning. Even this concentration maintained for 48 hours failed to effect a radical cure of benign tertian infection.

Malarial parasites are hæmosporidia and as far as is known live only in the red blood cells; they are not found in the plasma in a free condition or in the cells of the tissues.

The only occasion on which they are free is when the mature schizonts rupture and they attach themselves to fresh erythrocytes. It is possible that the cinchona alkaloids may destroy them in one of the following ways:—

(1) By making the erythrocytes distasteful for habitation of the parasite in the same way as *E. histolytica* will not ingest emetinised blood cells. The merozoites are in this way prevented from penetrating the red blood cells and perish because they are deprived of the only food they can live on.

(2) By parasitocidal action when the parasite is in the red cells. It has been said that the action is most marked on the youngest forms, less on the mature forms and very little on the gametocytes. Literature on the subject does not bear out the evidence that intra-corpuscular forms are any more vulnerable to quinine than the extra-corpuscular forms. Craig after careful study of the action of quinine on malarial parasites in fresh and stained specimens came to the conclusion that it affects the parasite injuriously in all stages in man except just prior to sporulation. Some of the recent work, however, throws doubt on the parasites being in the red corpuscles; there are some indications that they may lie on the surface.

(3) By the destruction of the merozoites when they are passing from one corpuscle to another. The sporulating body is not affected by quinine and sporulation occurs, but most of the spores are said to be destroyed by the drug in the blood plasma (Craig). The disappearance of the young forms indicates that they are the forms most vulnerable to the action of these alkaloids. Once the parasite gains entrance into the erythrocyte, probably schizogony can be completed in spite of quinine. This, however, is not the whole explanation, for if it were true, quinine would be much more efficacious during the time of sporulation.

(4) Morgenroth (1918) believed that malarial parasites are unable to enter red blood corpuscles which have been treated with quinine. It has been recently shown that quinine tends to condense on the surface of solutions, or at the interface, to such a degree that it forms a rigid film. If a tough film were formed on the blood corpuscles, this might protect

them mechanically against the entrance of the parasites. Bass (1921) suggested that quinine renders the erythrocytes permeable to the lytic action of the blood serum.

(5) By the formation of potent decomposition products in the body. It has been shown in the case of the organic arsenicals that the concentration required to kill the parasites outside the body appears much higher than the concentration which can be conceived to exist in the blood stream. This is attributed to their transformation into more effective compounds in the body. In the case of alkaloids like quinine, emetine, etc., the assumption of toxic transformation is so unsupported by the chemistry of these agents that it appears to be improbable. A substance named quinenine is formed from quinine by the action of the liver. Quinenine however has no action on the malarial parasites either in birds or in man. Quinine does not form any antimalarial compounds with the tissue on incubation. It appears probable that the parasitocidal effect is not a direct one.

Another characteristic of the cinchona alkaloids has been shown to be their property of interfering with certain enzyme reactions. This property of enzyme inhibition shows considerable selectivity which would be more consonant with the specificity of antimalarial action. This would then be conceived as interference with a metabolic process that is essential to the developmental cycle of the plasmodia.

It is quite possible that quinine acts mainly on the young forms in the course of their passage from one erythrocyte to another or when they are adherent to them or before they have actually penetrated into the red cells, *i.e.*, whilst the parasite is in contact with the alkaloids circulating in the plasma. Quinine and the other alkaloids of cinchona, even in high dilutions, inhibit the movements of malarial parasites and may even paralyse them. It is even possible that quinine may condense on the parasites and thus hinder their movements. This action may prevent the parasites from penetrating further into the red cells and thus deprive them of the only food they can live on.

The action of cinchona alkaloids on the gametes. Creasents appear suddenly in the peripheral blood on the 11th day

of disease, increase to a maximum and then decrease. The average duration of a crescent wave is 14 days, but crescents may persist for 66 to 128 days, when there are frequent relapses. Crescents are most plentiful in new cases and in relapses; and are fewer in number in chronic, latent and recrudescant malaria. In acute cases of malaria administration of quinine for short periods is said by some to favour the appearance of gametocytes in the peripheral blood. Two hypotheses have been advanced to account for this:—(1) That the administration of quinine expels the gametocytes from the deep viscera to the peripheral blood and (2) that it creates an environment which favours the development of increased numbers of gametocytes. According to others, quinine in the early stages does not increase but tends to inhibit crescent production.

The formation of resistant forms may be nature's method of self-preservation of the species and occurs in all forms of free-living unicellular organisms. When the environment is favourable so far as nutrition is concerned, multiplication takes place asexually; when the environment becomes unfavourable, the organism after conjugation assumes the cystic or resting stage until conditions are once more favourable for their asexual multiplication. On the other hand, many malariologists are now abandoning the view that crescent production is a response to unfavourable environment. Crescent production is at its maximum in infants and very young children who are extremely susceptible to malaria. Occasionally also, it may occur at the very beginning of an attack of subtertian malaria. When the gametocytes are present in the peripheral blood, the mosquitoes become infected.

The cinchona alkaloids have been shown to have little or no action on the gametocytes of malignant tertian parasites in the blood and only slight action on those of benign tertian. Administration of quinine however in doses of 20 to 30 grains a day reduces the number of crescents, probably by cutting off the source of supply by killing the asexual forms. According to James (1924) the development of gametocytes in all three species is not morphologically affected by quinine. The life of a red cell is said to be 30 days, though estimates

vary considerably; it follows therefore that crescents cannot live longer unless the dead red cells adhere to the crescents. Muhlen and Kirchbaum (1923) transmitted subtertian malaria through *A. maculipennis* to a fresh case, the donor at the time of infecting the mosquito being under the influence of quinine. It has also been shown that gametocytes developed under administration of quinine are viable. The gametocytes of malignant tertian type after administration of quinine will still be capable of infecting mosquitoes and spreading infection, although the patient himself may be freed from fever. On the other hand although quinine will not cure a benign tertian infection it will emasculate the benign gametocytes so that there is no risk of their passing on to others (Meyer and Wenyon). There is no other drug except plasmochin which has a direct action on the crescents and destroys them. Quinine in very low concentration stimulates metabolism and increases the rate of multiplication of parasites (Acton and Chopra 1927), but in the dilutions in which it circulates in the blood after therapeutic doses it decreases the rate of multiplication and therefore few merozoites will be formed.

Bass (1921) showed that quinine bihydrochloride in concentrations of 1 in 4,000 when incubated for 5 hours with the schizonts of *P. falciparum* may produce degeneration of the parasites. Direct action of quinine upon the plasmodia is however negatived by the observations made by Muhlen and Kirchbaum (1924) and later confirmed by other workers. It was shown that defibrinated tertian blood mixed with quinine hydrochloride in a strength of 1 in 5,000 still produced infection after 12 hours' exposure in patients suffering from general paralysis of the insane. The blood left for five hours in contact with 1 in 2,500 quinine hydrochloride will still infect these patients. Quinine given to the donor does not render the blood materially harmless to the recipient, and mosquitoes can be infected from the blood of patients taking quinine which shows that the action of quinine is indirect. Once the parasites enter the red blood corpuscles, they are not much affected by the action of quinine, and this is a point in favour of the paralytic theory of the merozoites. Clinicians know that when quinine is

administered after sporulation is completed, it does not prevent the next attack.

The mechanism of cure of malaria cannot, therefore, be by quinine acting directly on the parasites. Lipkin (1919) suggested that possibly a metabolite of quinine was the active agent. It has also been suggested that possibly an antigen from destroyed parasites stimulates immune-body production and helps to overcome the infection. Taliaferro, Krishnan and others have shown that the cells of the reticulo-endothelial system engulf and destroy the parasites directly and upon their number and functional efficiency depends the immunity in malaria.

Immunity production. One of the oldest theories of the production of cure, far older than Ehrlich's, was that remedies stimulate the resistance of the body cells in general, and so help them to overcome the disease or infection. This theory is vague and general, and so far as quinine is concerned, we know that it has so little effect on the tissue cells in general that it could scarcely be imagined to increase resistance. Moreover, the malarial invasion is so strictly confined to the red cells that general resistance would have little application. A more modern and definite version of the resistance theory is that the agents stimulate the production of immunising substances by the body cells. It would seem, however, that the effect of quinine is far too prompt to give opportunity for the manufacture of anti-bodies, which is rather a slow process. Another suggestion is that of the sensitisation of the parasites by the natural immune substances of the blood and tissues. The prompt action of quinine again suggests that the effect must concern the blood rather than the tissues. Besides, the failure of quinine, in reasonable concentration, to kill the parasites in the shed blood as shown by inoculation experiments, indicates that this is not the mechanism.

Yorke and Macfie (1924) believed that when quinine is given to a person with malarial infection, it destroys a large number of parasites but not all. A considerable amount of soluble antigen is set free and this provokes the tissues of the host to the formation of an immune body. The immune body when present in sufficient amount, destroys the remaining parasites, producing sterilisation of the infection and the cure of the patient. This is supported by the fact that it is very difficult to infect some people with injection of blood containing living parasites. If, for any reason, there is an insufficient production of the antibody, sterilisation does not take place and a relapse will occur. Auto-hæmotherapy, that is drawing of the patient's own blood and injecting it subcutaneously, has been suggested in the treatment of malaria, the idea being that the parasites present in the blood will

die and act in the same way as a vaccine does. Sometimes parasites though reacting to quinine, may become resistant to the immune body, with the result that constant relapses occur. James (1928) believed that quinine continued for too long after an attack may interfere with the formation of the immune body. Cicmsa (1937) concluded that it must be accepted that quinine acts directly on the malarial parasites to which it is anchored and which it poisons. It is incapable of manufacturing a specific immune body, but it is nevertheless possibly favoured by its presence. Ross (1927) showed that in malignant tertian infections the parasite-containing corpuscles are lysed by the action of quinine with the formation of bilirubin, the amount of which in the blood is thus temporarily increased; it falls to normal as the parasites disappear from the blood.

It would appear from the above that it is not quite clear as to how a specific drug like quinine destroys the malarial parasites and produces a cure of this disease. All the facts at our disposal show that the action of quinine is probably not a direct one on the malaria parasites.

CHAPTER XXII

PROPHYLAXIS AGAINST MALARIA

As the eradication of malaria from malarious districts is a very difficult matter, attention has been paid to the prevention of the disease in individuals. This problem can be considered under three headings:—

(1) **Measures concerned with infected persons.** The segregation or isolation of malarial patients has been suggested, but in practice it is difficult to carry out. The disinfection of infected persons with quinine is not practicable, though with the introduction of plasmoquin, it may prove possible in the future to control epidemic malaria by mass administration of plasmoquin as a 'crescenticide'. Wholesale cinchonisation of infected persons to kill the parasites in the human host and so prevent the mosquitoes from becoming infected has been suggested, but it is now known that it is very difficult to destroy the gametocytes of malignant tertian with quinine after they have appeared in the circulation. The best measures which can be adopted are as early and as thorough a treatment as possible with a view to destroying the quinine-susceptible or asexual forms and preventing, as far as possible, the production of quinine resistant or sexual forms. Plasmoquin destroys the sexual forms of malarial parasites and is more suited for this purpose. If the cases remain infective, screening should be tried so that mosquitoes do not come in contact with the infected individual. If mosquito-proof houses are not possible, use of mosquito nets may be practicable.

Anti-relapse measures are important and they can be divided into three groups. (a) Administration of cinchona alkaloids. Any of the methods of treatment already suggested may be employed. (b) General measures, such as avoidance of fatigue, too long exposure to heat or cold and anything which lowers body temperature and may bring about a relapse, should be advised. (c) Removal of the patient to a better climate if that is possible.

(2) **Measures concerned with the transmitting mosquitoes.** These consist of destroying the mosquito by means of insecticidal drugs. *Paris green* keeps down the number of mosquito larvæ and has been largely used.

(3) **Measures connected with the susceptible person.** These consist of avoiding exposure to infection, *e.g.*, by guarding against mosquito bites and by taking quinine as a prophylactic measure.

Quinine prophylaxis. By this is meant taking of quinine in such a manner, as to prevent attacks of malaria, not by quinine acting on the sporozoites, but by preventing the multiplication of the parasites into which sporozoites develop. It really means that the body will have quinine circulating in the blood in such a manner as to anticipate the first dose of sporozoites injected by the mosquito. It does not prevent infection, but cures an attack by killing the parasites after infection has taken place, or reduces the degree of infection to such an extent that an otherwise dangerous infection is rendered mild and comparatively a harmless one. The incubation period of malaria is 12 to 14 days. Administration of the drug before infection does not produce any effect. It may be that, in spite of quinine, sporozoites still enter the red blood corpuscles and that quinine acts by killing the early stages of the parasites in the erythrocytes or the trophozoites when they are liberated. York and Macfie (1924) showed that under experimental conditions 18 grains of quinine daily for 5 days before and 7 days after bites by infected anopheles failed to avert an attack of malaria, but if the drug was continued for 10 days after the insect bite the disease did not develop. This indicates that quinine has little effect on the injected sporozoites but acts on the asexual forms liberated from the red blood corpuscles. Weber noted that quinine given to a disinfected donor did not render his blood non-infective to susceptible recipients, showing thereby that the blood must have contained some parasites which resisted the action of the drug.

It has already been pointed out that quinine acts more readily on the gametocytes of the benign tertian parasite than on those of the malignant tertian and therefore mosquitoes are more

readily infected from malignant tertian cases taking quinine than from benign tertian cases. If however quinine is not administered, benign tertian cases much more readily infect mosquitoes than the malignant tertian cases. *Anopheles* mosquitoes have been infected by feeding on the blood of patients taking quinine, thus showing that the benign tertian gametocytes are not killed by the action of the drug. It would appear from this that as quinine does not affect the entrance of the parasites into the blood, nor the development of the sporozoites in the red blood corpuscles in the early stages, it cannot therefore be regarded literally as a prophylactic against malarial infection. The drug probably acts chiefly by paralysing the movements of the trophozoites. The Malaria Commission of the League of Nations (1927) pointed out that quinine taken over a sufficient period of time and in appropriate doses can often prevent the appearance of symptoms, thus enabling the organism to rid itself of the parasites. It is not possible to store up quinine in the body ready to attack the malarial parasites when they gain entrance into it. It is useless, therefore, to give quinine in the pre-epidemic period; a start should only be made when the risk of infection arises. There is thus no advantage in giving quinine as a prophylactic to people going to very malarious countries before their arrival there. In countries with comparatively low incidence where malaria is often of the benign type, the continued use of quinine as a preventive of malarial attacks has little place. In countries where most of the indigenous population is infected with malignant tertian parasites, it is probable that 5 to 10 grains of quinine taken daily will not prevent the patient from contracting malaria but will render the attack of malaria, when it supervenes, so mild that the patient can still remain on duty.

There has been a lot of difference of opinion, lately, regarding the employment of quinine as a prophylactic measure. As long ago as 1760 Europeans living in the Guinea coast used cinchona bark powders continuously during the rainy and unhealthy seasons. The advisability of this is supported by much modern experience, although of late years there has been a distinct feeling against the prophylactic use of quinine, chiefly

on account of the experience during the Great War. Alport (1919) found that in Salonika 15 grains of quinine twice weekly did not prevent the soldiers from getting infected with malaria. He says that to submit healthy individuals to treatment such as this for long periods makes prevention worse than cure. On the other hand good results are reported from prophylactic doses of quinine. In the Belgian Congo it was found that 15 grains of quinine twice a week rendered the infections mild and few, only 0.3 per cent. of the working days being lost. Even those taking quinine only once a week for a year had considerably less infection at the end than at the beginning of the period. In Liberia 1 gm. of quinine on Sunday and 1 gm. in the middle of the week practically stopped the occurrence of blackwater fever. In Algiers it was found that daily doses of quinine rendered the attack milder and minimised the danger of the infected person becoming a carrier. The usual causes of failure are connected with dosage, method of administration and the amount of responsible supervision.

Hodgson was the first to point out that the incidence of malaria was closely correlated with minimum wet bulb temperature and he noticed in Delhi that a marked increase in malaria occurred a fortnight after this temperature reached a certain limit, not exactly determined, but probably 18° to 20°C . This increase continued as long as this temperature was maintained, but if it rose above or fell below these limits, a fortnight later the incidence diminished. The reason why minimum temperature affects the incidence of malaria is that anopheles usually bite during the early part of the night and digestion of red blood cells takes place some hours later. Flagellation of the male gametocyte takes place in the presence of moisture and occurs at a temperature between 18 to 22°C ; temperatures above and below these points hinder flagellation and, therefore, fertilisation of female gametes does not take place and without this the female gametes of malarial parasites cannot undergo their extracorporeal cycle in the mosquito for the sporozoites to be transmitted to the host. The temperature of cold-blooded animals like mosquitoes corresponds approximately to the wet bulb thermometer. According to this view prophylactic quinine should be given with due regard to seasonal variations of the temperature. It should be given when infection begins, i.e., when the minimum wet bulb approaches the point when flagellation of male gamete commences, and stopped when this ceases.*

The next important question is whether quinine for prophylactic purposes should be taken daily or intermittently and at what time it should be taken. Various methods of administering quinine prophylactically have been suggested:—

Koch gives 15 to 22.5 grains on two consecutive days at intervals of 8 to 11 days. This method is known as the long interval prophylaxis and is not considered safe. Plehn gives 7 to 8 grains every 4th and 5th or 5th and 6th day. This is known as the method of double prophylaxis. In India usually 10 grains are given twice a week on two consecutive days.

Hehir suggests 5 grains daily for six consecutive days in the week when malaria in a locality is of mild type; when it is moderately severe, 10 grains are also given on the 7th day. If malaria is of severe type or occurs in epidemic form, the doses are doubled, *i.e.*, 10 grains a day for 6 days and 20 grains on the 7th day. In children one grain of quinine or $1\frac{1}{2}$ grains of euquinine for every 3 years of age is sufficient. In all cases the dose is usually given in the evening. Some authorities have suggested 5 grains of quinine in solution about an hour before sunset and a second dose of 5 grains about midnight in places where a severe type of malaria prevails. Even such doses as suggested above may not ward off the paroxysms in some places where malaria is severe. When the numbers of infected anophelines are small, comparatively few sporozoites reach the blood. It has not been possible to ascertain the minimum quantity of quinine necessary to destroy the young trophozoites developed from these sporozoites, but we know by experience that the minimum dose in an ordinary endemic year would not be sufficient in an epidemic year or even in a year of high endemicity. A larger dose is required in the late autumn than in early summer or midsummer. Failure may be due to the fact that a heavy infection had taken place before the prophylaxis was started. The optimum prophylactic dose of quinine to keep all men free from a harmful number of parasites has not been ascertained. Quinine prophylaxis would be more effective if controlled by periodic blood examinations, because this may discover some infection nearing sporulation when curative doses of quinine have a value.

Some prefer quinine in the form of solution but tablets are much more convenient. Ramsden's experiments have shown that after a single dose of quinine the time of excretion is 4 to 8 hours but the elimination goes on for 24 to 48 hours; when a series of doses is taken complete elimination takes $7\frac{1}{2}$ days. From these facts one is justified in concluding that continuous doses are the best. As quinine is not fully eliminated from the body within 24 hours, the dose may be given every other day, but daily administration would be the best. It has been shown on a small scale, that 5 grains of quinine daily reduce the attacks by 20 per cent.; 10 grains daily by 56 per cent.; 15 grains a day by 70 to 80 per cent.; but even 15 grains a day will not always prevent malarial infection. When malarial infection has occurred and paroxysms are produced larger doses should be given.

A further interesting fact is that in countries like India benign tertian infections occur commonly at the beginning and malignant tertian at the end of the hot weather, extending well into the winter months—November and December. This is due to the fact that infected anophelines are on the wing for weeks after their breeding season. To obtain the best results, therefore, prophylactic doses of quinine will have to be given practically all the year round with the exception of two or three months in the winter. It might appear from this that other preventive measures such as mosquito-proof houses, the use of mosquito nets, electric fans, well-built freely ventilated houses and proper drainage would be preferable wherever possible.

It has been stated that those habitually taking small doses of quinine as a prophylactic are very difficult to treat when they get infected, as the parasites become quinine resistant and in these people the disease becomes chronic. It has already been said that resistance of parasites to quinine is not probable. Chronic malaria, as a rule, does not develop when prophylactic quinine is being taken. Infection probably occurs from the lowering of the resistance of the individual and the dose which stops the paroxysms when the patient is strong will not do so when his vitality is enfeebled. It is necessary to increase the dose when such factors as fatigue, hardship and exposure, which lessen the resisting power of the individual, are encountered. Rigid adherence to one particular dose, *e.g.*, 10 grains twice a week, when the disease is of a virulent type accounts for failure of prophylaxis. Prophylactic dose of quinine which will prevent attacks in an individual with some degree of immunity will not be sufficient in case of non-immune fresh arrivals. This is borne out by the experience of Military Medical Officers in the Indian cantonments where the arrival of non-immunes may greatly intensify the endemicity of the whole area. They get the infection first and then infect anophelines in large numbers, thus establishing a vicious circle which is only broken when immunity is developed in the new-comers. The Report of the Malaria Commission

of the League of Nations has stressed the importance of the production of epidemics by immigrants who have no immunity against malarial infections.

Eradication of malaria from a large population was tried in Formosa with a certain degree of success by giving all the infected persons a thirty day course of quinine. In Switzerland and Corsica, extensive quinisation of the population has reduced the incidence of malaria in many districts. In the Dutch East Indies quinisation of the population has been tried, especially in the schools. In Palestine regular administration of 30 grains daily for 5 days, followed by 10 grains daily until the end of the malarial season, reduced the loss of working days to one-sixth. Even after prolonged quinisation one-fourth of the patients had parasites in the blood within four days of ceasing quinine, showing that the infection was merely masked and not eradicated. Quinine prophylaxis, unless associated with the destruction of anopheline mosquitoes, will not render an area entirely free from malarial infection.

Briefly then, the position of the prophylactic use of quinine against malaria is as follows:—Prolonged prophylactic use of quinine is a curative rather than a preventive measure. The dose should be sufficient to kill all parasites which develop in the blood from day to day. On the sporozoites it has no effect, and it only acts on the trophozoites when they are liberated from the red blood cells. It is advisable to take it in doses of 5 grains or better $7\frac{1}{2}$ to 10 grains daily in those areas where a large proportion of the indigenous population is infected with malignant tertian parasites, as in tropical Africa; this is the only sure way of averting attacks of pernicious malaria. Large doses may be necessary where a severe type of malaria prevails or an epidemic is present. On the other hand, in countries with comparatively low incidence, mainly of benign tertian type, the continued use of quinine as a preventive of serious malarial attacks will find little place in the so-called prophylaxis against the disease. Although quinine is no absolute protection against infection, it renders the attacks milder and less frequent and it lowers the mortality rate and spread of infection. The degree of success of prophylactic use of quinine depends on the control and distribution of the drug. Although malaria cannot be eradicated it can be kept under control by continued use of protective measures, as in the Panama-Canal Zone.

CHAPTER XXIII

QUININE IN BLACKWATER FEVER AND OTHER AFFECTIONS

Blackwater fever. Although the ætiology of blackwater fever is still undecided there is general agreement that malignant tertian malaria is always associated as a predisposing cause. It is a complication of malaria, occurring mostly in hyperendemic areas. Blackwater fever occurs in Central Europe, from Spain to the Balkans; in Turkey and Palestine; in such malarious parts of India as Assam, Bengal and the Dooars; throughout the tropical and sub-tropical parts of Africa from Algeria to Abyssinia and Rhodesia, Mauritius, Madagascar, the Southern United States, the West Indies and South America. The disease is very rare in mountains, but is common in the country and forest areas. It tends to recur in the same houses when they are near the breeding grounds of anophelines. Malarial parasites occur in over 73 per cent. of cases, generally *P. falciparum* is present but the infection may be mixed. *P. vivax* and occasionally *P. malariae* have also been found. One attack of blackwater fever predisposes to another attack so that as many as 13 attacks have been recorded but without any tendency to increased severity of the later attacks. Spirochaetes are said to have been found in the blood; but this has not been confirmed. The simplest and most widely held theory about its causation is that as the result of repeated destruction of red blood corpuscles owing to recurrent attacks of malaria, a hæmolysin is formed and hæmolysis is produced in the same way as by the injection of foreign blood into animals. It is asserted that the products of chemical changes brought about in the corpuscles due to the presence of the plasmodia act like a foreign material. The destruction of the red blood corpuscles occurs in the kidneys and probably in the peripheral blood as well. No hæmolysin has however been demonstrated in the blood.

The disease commences with a definite rigor and passage of dark urine, which may last several hours or several days. The blood shows marked anæmia, polychromasia and punctate basophilia. The large mononuclear cells increase to 20 per cent. or more and there is a marked shift to the left of the Arneth index. The spleen is enlarged soft and pigmented; the kidneys are enlarged, deeply pigmented with dark granular casts and degeneration of epithelium of the convoluted tubules; the heart shows fatty degeneration.

In India blackwater fever appears to be always associated with four pre-determining factors, *viz.*—

(i) The presence within half a mile of an aboriginal population saturated with malaria. This aboriginal population has become immune or tolerant to the infection, but the malaria strain concerned is one of intense virulence. The aborigines themselves do not get blackwater fever.

(ii) The disease attacks only the susceptible immigrants, such as Europeans, Chinese carpenters, Bengali clerks, and their families.

(iii) The presence of anophelines of the *funestus* group.

(iv) Usually, but not necessarily always, the irregular taking of quinine over considerable periods. Blackwater, however, is not always and inevitably associated with taking quinine. In the monkey *Silenus trus* inoculated with the monkey plasmodium *Plasmodium knowlesi*, blackwater occurs as a terminal event in the fever, in the absence of any quinine administration. This is probably due to the terrific intensity of the infection in this species of monkey.

Many poisons are known which attack the blood corpuscles and destroy them. Quinine, in concentrations in which it occurs in the blood does not destroy red cells, and yet many authorities have laid stress on its association with this disease. Neither clinical history nor animal experiments tend to show that quinine is the cause of it. Blackwater fever was known to exist in Europe long before quinine was introduced. Bi-hydrochloride of quinine has a hæmolytic action on the erythrocytes, but during life it is not possible to reach a sufficiently high concentration in the blood to produce it. Some observers think that quinine produces hæmolysis by lowering the osmotic pressure of the plasma, which causes water to pass into the red blood corpuscles which swell up and burst. Nierenstein (1919) isolated a derivative of quinine, hæmoquinic acid, from the urine of cases of blackwater fever. Manson pointed out that hæmoglobinuria could be produced in certain cases by the administration of a single dose of quinine. An instance has been recorded of seven consecutive attacks of hæmoglobinuria in the same individual, each attack being a sequel to a dose of quinine. Such small doses as 5 grains by the mouth

brought on an attack. Such cases do not necessarily show increased vulnerability of the red cells to the hæmolytic action of quinine *in vitro*. No evidence of any hæmolysin in the peripheral blood has been found by some workers while Chiron (1927) claimed to have demonstrated its presence. Manson-Bahr and Sayer suggest that quinine may possibly excite blackwater fever by inducing a sudden contraction of the spleen which expels hæmolytic toxin into circulation. Garrod regards cold as a most potent factor in its production in patients suffering from malignant tertian infection and considers that quinine is not essential in causing an attack, but is a contributory factor. According to him, patients treated with very large doses of quinine, are not more liable to an attack. Increase of lactic acid in the blood owing to deficient oxygenation such as occurs in anæmia is suggested as the cause of hæmoglobinuria; lactic acid has a hæmolytic action on the blood *in vivo* and *in vitro*. It is also suggested by him that in the presence of bile, quinine becomes highly hæmolytic and some undetermined constituent of the bile renders quinine hæmolytic in one-tenth of the concentration usually required. Disturbed function of the liver has been put down as the cause of blackwater fever. Kessler (1925) showed that lecithin increases the hæmolytic action of quinine on the blood *in vitro*. It has also been shown that in blackwater fever the degree of bilirubinæmia is much greater than in uncomplicated malignant tertian malaria. It is assumed that some such substance is liberated in the blood by repeated attacks of malaria and produces the symptoms. Other authorities have suggested that the presence of a foreign protein resulting from destruction of merozoites induces an anaphylactic phenomenon. But blackwater fever has nothing in common with anaphylaxis. Hyperactivity of the reticulo-endothelial system, due to repeated attacks of malaria with consequent hæmoglobinuria, is another theory. It is now recognised that proper administration of quinine prevents the occurrence of blackwater fever; but once an individual is predisposed to blackwater fever by repeated attacks of neglected malaria, full doses of quinine may act as an exciting cause in precipitating hæmoglobinuria.

The causation of this condition has been thought to be:—

- (1) An underlying condition of a very chronic malarial infection. This is not the entire reason as otherwise it would be more commonly met with; besides it is quite safe to give quinine in malarial cachexias without causing hæmoglobinuria. In certain districts of the Punjab where malarial conditions are ideal as regards malignant tertian infections, no hæmoglobinuria is met with. The disease is however limited to areas in which malaria occurs not only endemically but in

severe forms. During or preceding the attacks, malarial parasites are frequently found in a large number of cases and there is a relative increase of the large mononuclears with increase of pigment in the corpuscles. (2) Some undiscovered specific poison, like that causing 'Texas red-water fever' in cattle (*Piroplasma bigeminum*). (3) A form of quinine poisoning. Administration of quinine could only be the determining cause in those cases which have an idiosyncrasy or intolerance for the drug. The condition of the blood in these individuals is such as to foster the destruction of the red blood cells. Apart from quinine intolerance, that there is a critical exciting dose of quinine, varying in different individuals, which may bring about an attack in some cases, is very definite. It is believed that for certain patients there is a critical dose, in whom quantities smaller than that causing it should, therefore, be prescribed. If hæmoglobinuria occurs, administration of quinine should be immediately stopped. Some authorities believe that if alkalies such as bicarbonates are given with quinine treatment, blackwater fever does not occur.

From these considerations it will be seen that the whole subject requires further research. That both malarial hæmoglobinuria and quinine hæmoglobinuria exist is certain, but blackwater fever may be a specific disease due probably to some such organism as a piroplasma. In the author's experience in British East Africa two groups of these cases were differentiated. (1) In which malarial parasites occurred in large numbers. (2) In which they were entirely absent, this was the more severe type producing a very high mortality. Quinine produced immediate good effect in the former class and also when the parasites reappeared after an attack, which is usually 5 to 14 days after cessation of hæmoglobinuria. In the second group of cases quinine had no effect. Whether this latter group was produced by any specific organism or whether it was a later stage of the first where all the parasites had disappeared from the blood, has not been determined. In ordinary cases administration of quinine after the attack does not lead to hæmoglobinuria, but if there is a history of predisposition to such an attack it should be given with great caution. The amount of

quinine which can be administered to these patients depends on the quantity of urine passed in 24 hours, because if the kidneys are unable to excrete a sufficient amount of urine to get rid of the quinine, it accumulates in the body and gives rise to symptoms of quinine poisoning such as amaurosis. Caution should therefore be exercised, especially in the acute stages of the disease when it is necessary on the one hand to destroy the malarial parasites, and on the other hand to see that the quinine is being excreted through the kidneys. Quinine acts first on the infected red corpuscles and hæmolyses them so that the parasites disappear from the peripheral blood. It is better to start with small doses, *e.g.*, 1 to 2 grains several times a day and only to increase them when it is clear that the drug is being well tolerated, for occasionally even with such small doses hæmolysis may occur. Administration of large doses of alkali with quinine is beneficial. Whenever malarial parasites are found to be present in blood, quinine should be given at once. This occurs 5 to 14 days after the urine has cleared, and it has been shown that parasites may be found in the internal organs in fatal cases after death, and yet may be absent in the peripheral blood during life. The prophylactic use of quinine in endemic areas, though it does not prevent infections, stops their becoming severe or pernicious, and by maintaining health acts as a true prophylactic against blackwater fever. Plasmochin has been tried with success in a number of cases of blackwater fever.

As regards the general treatment of these cases the patient should be put to bed at once and should not be allowed to sit up as there is danger of sudden heart failure ; absolute rest is essential. When the urine tends to be suppressed caffeine citrate 2 grains twice daily may be given as a non-irritating diuretic. The patient should have plenty of bland fluid and an exclusive milk diet until the urine is free from albumin. Hot fomentations over the loins or dry cupping may be useful. High rectal lavage with hot water has a diuretic effect. Hypertonic saline containing 120 grains of sodium chloride and 4 grains of calcium chloride in a pint of sterile water is recommended. If vomiting is present give enemata of 6 to 8 ounces of warm saline

and also saline subcutaneously. Five grammes of sodium bicarbonate in a tumblerful of hot water should be taken frequently. If there are convulsions, give 5 per cent. solution of glucose in 1-2 pints of saline intravenously. In case of restlessness give $\frac{1}{4}$ grain of morphine. Injection of antivenomous and other serums has been recommended. Activated horse serum is also useful. Iron and arsenic should be prescribed during convalescence. Recently, cholesterinated oil has been recommended in the treatment of this condition.

QUININE IN OTHER CONDITIONS

Pneumonia. Quinine was used in the treatment of pneumonia for over half a century ago. Aufrecht (1915) claimed that quinine has a specific action in pneumonia and by its consistent use mortality could be reduced. Boecker (1921) found strikingly large quantities of quinine in the lungs and in the expectoration of consumptives after its administration by the mouth. The pneumonic lung 4 days after injection, still contains quinine in higher concentration than is ever found in the blood. Statistics have been compiled to show that the mortality in the patients treated with quinine is much lower than those not treated with this alkaloid. Quinine should be given as early in the disease as possible. Continuous treatment with small doses every 2 or 3 hours is the best. It is inimical to the progress of most acute infections and in the case of pneumonia it is said to limit the spread of consolidation, thus altering the whole aspect of the disease. Calomel should be given to clear the bowels, and quinine may be combined with such an aperient as sodium sulphate. Intramuscular injections of quinine hydrochloride 0.50 gm., urethane 0.25 gm. and water 5.0 c.cm. have been recommended. This solution can be boiled. The patient is given an injection at once on the day of admission, one on the following day and afterwards every second day, but as a rule not more than four injections are necessary. Quinine in pneumonia finds no place now in practical therapeutics.

Common cold and influenza. Quinine is often used in the treatment of the common cold. It cannot reach the mucous membrane in strengths sufficient to produce antiseptic effects but it probably acts as a sedative. It has also been tried in influenza as a prophylactic, and for treatment in doses of 0.3 gm. once or twice a day.

Puerperal septicaemia and other conditions. Puerperal septicaemia has been treated with 2 grains of quinine every few hours. Quinine has also been used in any form of suppuration in the body *e.g.*, perityphlitic abscess, gall bladder abscess, empyema, bone and

joint disease. Prior to and immediately after operation. It is also recommended in erysipelas.

Exophthalmic goitre. Quinine and cinchona alkaloids are useful in this condition because of their vaso-constrictor properties on some vessels and secondly because of their effect on the heart. Besides this quinine retards all vital processes, it inhibits the conversion of glycogen into sugar and also limits protein metabolism. For this reason it has a beneficial effect in this disease where, owing to increased activity of the thyroid, the metabolism is markedly accelerated. A dose of 0.8 gm. of quinine is given in two portions and increased gradually every day. As soon as tinnitus begins the patient goes to bed. The alkaloid is continued for 8 days after which there is a rest for 8 days. This is repeated until the clinical symptoms, *e.g.*, pulse, exophthalmos, etc., improve. Quinine is subsequently given for three days in the week. The effect of quinine is said to be strengthened by combining it with 30 minims of extract of ergot

Diseases of the circulatory system. Quinine has had the reputation for being a cardiac sedative for a long time. Upolzer considers that along with rest and digitalis it is one of the three most powerful therapeutic agents in heart disease. It is said to have a damping effect on excessive digitalis action and is therefore often combined with it. It is claimed that a mixture of digitalis and quinine produces better effects than digitalis alone. Quinine and quinidine have a powerful action in controlling cardiac arrhythmia and irregularities. These should however be used with great caution when there is true weakness owing to myocardial disease.

Other conditions. In lumbago, injections of quinine-urea-hydrochloride relieve pain. In the treatment of sciatica, injections of quinine-urea-hydrochloride into or about the sciatic nerve are recommended. One per cent. solution is generally used and 15 to 30 c.cm. are injected at the point where the nerve lies over the neck of femur. The patient lies on the unaffected side with the affected thigh half-flexed. A point is selected somewhat lateral from the midpoint. The needle is pushed in for 3 to 4 inches and when it strikes the nerve a smarting pain is felt down the leg.

On account of its diuretic effect it is said to be very useful in certain forms of cedema and dropsy, especially those due to anæmia and cachectic conditions.

Quinine in 1 to 2 grain doses has been used with beneficial results in cases of vertigo combined with migraine. *Hæmorrhoids* have been treated by injections of a 5 to 10 per cent. solution of quinine-urea-hydrochloride. A perivenous sclerosis is said to be produced which progressively constricts the veins. The injections are entirely painless.

In the treatment of *varicose veins* intravenous injections of quinine into the local veins are employed. The drug acts (1) by reducing the

time of coagulation of blood and (2) by irritating the wall of the vein and producing thrombi which become firmly attached to the vessel. The solution recommended is quinine hydrochloride 0.40 gm., urethane 0.20 gm. and distilled water 3 c.cm. One to 3 c.cm. of this are given locally into the varicose veins.

Pruritis ani, vulvæ and scroti have been treated by infiltration of the skin and subcutaneous tissue with 0.25 to 0.5 per cent. quinine urea hydrochloride. Itching is at once arrested and excoriations rapidly healed. One injection may suffice to keep down the condition for months. As much as 100 to 200 c.cm. of the solution may be necessary.

Venereal diseases. Quinine has been used as a prophylactic against contracting venereal diseases, because of its bactericidal action on the gonococci and spirocheticidal action. It is often combined with calomel and gelatine in a strength of 2.5 to 15 per cent.

Induction of labour with quinine. Quinine has been used for many years as a means of re-enforcing uterine contractions, especially when they are not strong. Most authorities agree that in therapeutic doses it does not excite the activity of the quiescent gravid uterus and therefore, it cannot be relied on for inducing premature labour. If however weak contractions are present they are intensified. The greater the tone and activity of the uterus the more rapid is the action of quinine. It is considered by some to be safer and its action more persistent than pituitrin. Various methods of giving quinine have been adopted.

Watson's method. Castor oil one ounce at 6 p.m., quinine hydrochloride 10 grains at 7 p.m., enema at 8 p.m., quinine hydrochloride 10 grains at 9 p.m., and again at midnight. If labour pains do not start by 7 a.m., on the next day, give $\frac{1}{2}$ c.cm. of pituitrin intramuscularly and repeat every half an hour till labour commences. Balley (1926) recommends 2 ounces of castor oil to start with, and an hour after, $\frac{1}{2}$ an ounce of quinine mixture containing 10 grains to the ounce. After one hour a simple enema is given. Two hours after the enema another dose of the mixture is given, this is repeated after 3 hours and then four hours later, making a total of 40 grains of quinine. The percentage of success with this treatment is greater than with pituitrin and the danger is less.

Quinine as a contraceptive. Quinine has been used as a contraceptive in clinical practice for a long time but during recent years it has been replaced by other drugs.

CHAPTER XXIV

PREPARATIONS OF CINCHONA BARK AND ITS ALKALOIDS

Cinchona Bark, dose 5 to 15 grains. **Extract cinchona** (contains 10 per cent. total alkaloids) dose 2 to 8 grains. **Extract cinchona liquid** (contains $\frac{1}{2}$ gr. of the alkaloids in 15 minims). Dose 5 to 15 minims. **Compound tincture of cinchona** (contains 0.5 per cent. of total alkaloids), dose $\frac{1}{2}$ to 1 drachm (2 to 4 c.cm.). **Cinchona febrifuge** is a mixture of the total alkaloids of cinchona bark of varying composition. It has been extensively used in India for the last 50 years with satisfactory results. It is cheap and suitable for mass treatment. It has recently been standardised by the Malaria Commission of the League of Nations.

Totaquina. A mixture of the alkaloids from the bark of *Cinchona succirubra* and other species of cinchona. It contains not less than 70 per cent. of crystallisable cinchona alkaloids, of which not less than $\frac{1}{5}$ th is quinine. Dose 1 to 10 grains.

CINCHONA ALKALOIDS AND THEIR PREPARATIONS

A. Crystalline alkaloids.

Quinine hydrobromide occurs in white acicular crystals, soluble 1 in 40 of water and contains 76.6 per cent. of quinine. It is said to lessen cinchonism and is valuable in acute rheumatism. Dose 5 to 15 gr. **Quinine bihydrobromide** contains 60 per cent. of quinine, soluble 1 in 7 of water and is suitable for subcutaneous and intravenous injections. It is non-irritating and the additional hydrobromic radicle tends to prevent cinchonism. Dose 5 to 10 grains.

Quinine hydrochloride contains 81.7 per cent. of base. Solubility 1 in 32 of water and in 1 in 2 of 90 per cent. alcohol; used for subcutaneous injections. Dose 1 to 10 gr. It is mixed with theobroma oil and forms a part of many contraceptive preparations. Quinine hydrochloride is contained in **Tincture quinine**, the dose of which is $\frac{1}{2}$ to 1 drachm and **Vinum quinine**, dose $\frac{1}{2}$ to 1 ounce.

Quinine bihydrochloride contains 81.6 per cent. of quinine; solubility 1 in 0.6 of water. It is considered a good salt for intramuscular and intravenous injections; the hydrochloride radicle is also not as irritating as the sulphuric radicle to the stomach. Dose 1 to 10 gr. For intravenous injections some use 1 to 300 solution, others 10 per cent. solution. Half to 1 per cent. produces local anaesthesia when

injected; for painting on mucous membrane 10 per cent. solution is the best. Sterules of various sizes are on the market.

Quinine hydrochloro-carbamide or urea-quinine occurs in small prisms; solubility 1 in 1 of water, contains 59.2 per cent. of quinine. Dose 5 to 15 gr. Used to produce local anæsthesia in 1 to 3 per cent. solutions; anæsthesia persists from 4 to 6 hours to several days.

Quinine hydriodide and **acid hydriodide**, **quinine hypophosphite** and **quinine lactate** are some of the salts which are not much used.

Quinine phosphate contains 72.8 per cent. of quinine base. Dose 1 to 6 gr.

Quinine salicylate occurs in white crystals; sparingly soluble in water; contains 68.8 per cent. of quinine base. Useful in sore throat.

Quinine acetyl salicylate contains 64.3 per cent. of quinine. It is a useful antipyretic and antiseptic compound. Dose 1 to 5 gr. It is prescribed in painful sore throat.

Quinine sulphate contains 73.5 per cent. of quinine base. Dose 1 to 15 gr. It occurs in white crystals, solubility 1 in 800 of water. It occurs in a number of preparations. **Ammoniated tincture of quinine** is a solution in 60 per cent. alcohol to which ammonia is added; the precipitate formed is suspended in tragacanth. **Quinine bisulphate**. Dose 1 to 10 gr.

Quinine tannate contains 30 to 35 per cent. of quinine base. It is tasteless and is recommended for children. Absorption is uncertain. It splits up slowly in the intestine and is therefore not prompt in its action. Dose $1\frac{1}{2}$ to 15 gr.

Quinine arsenate, dose $\frac{1}{2}$ to $\frac{3}{4}$ gr., occurs in small white crystals sparingly soluble in water; contains 15.2 per cent. of arsenic acid and 69.4 per cent. of quinine. **Quinine cacodylate** given *per os* and subcutaneously; dose $1\frac{1}{2}$ to 4 grains. **Quinine citrate**, dose 1 to 5 gr. **Iron and quinine citrate**, dose 5 to 15 gr.

Quinine ethylcarbonate or **euquinine** occurs in white needles having a melting point not below 95°C. It is sparingly soluble in water but is more so by addition of dilute acid, easily soluble in alcohol. It is practically tasteless. Eight grains of euquinine are equivalent to 5 grains of quinine sulphate. It is rapidly absorbed and appears in the urine soon after injection. Dose 3 to 16 grains.

Aristo-quinine or **aristochin** is insoluble in water and is tasteless. It contains 96.1 per cent. of quinine. Dose 1 to 10 gr. It has been used against malaria, influenza, and in small doses in pertussis.

Soloquinine is the name given to quinine salicylic ester.

Chenophenin is phenetidin-quinine-carbonic ester. Both these compounds exhibit the action of both the constituents of the drug. **Collobiase of Quinine** is a preparation in which quinine is kept in a colloidal state in combination with arabinic acid. It contains 30 per cent. of quinine base. It can be given intravenously and subcutaneously.

Collosol quinine or the alkaloid in colloidal condition has been introduced.

Tests for quinine.

1. *Fluorescence.* The alkaloid is dissolved in dilute sulphuric, acetic or tartaric acid (the test tubes should be made of transparent glass or silica). One mgm. of quinine can easily be detected in 4 c.cm. of solution. Fluorescence is visible in acid solution containing 1 in 200,000 of quinine. The fluorescence may be masked by the presence of chlorides and hence the test is not a very useful one.

2. *'Thalletoquin' reaction.* To 10 c.cm. of the solution of quinine add 3 c.cm. of chlorine water or 0.5 c.cm. of saturated bromine water. Shake well, and then add one drop of strong ammonia solution or sufficient to render the liquid distinctly alkaline. If the proportion of quinine exceeds about 1 per 1000, a green substance is precipitated. In more dilute solutions, a deep green colouration is produced. One in 5,000 quinine solution is detected by this test and if bromine is used instead of chlorine, quinine can be detected in a still higher dilution (1 in 20,000). This test is given by quinine, quinidine, and the hydroquinine alkaloids, and the decomposition products quinotoxin and quitenine. The cupreine series also give this test. It is not given by the members of the cinchonine series or their decomposition products. In 10 c.cm. of solution 0.25 mgm. of quinine can be detected with ease.

3. *Herapathite reaction* (Ramsden and Lipkin). (1) To 10 c.cm. of test solution add 5 gm. of $(\text{NH}_4)_2\text{SO}_4$, alkaline it with ammonia and extract the quinine by shaking it with three successive 5 c.cm. lots of purified ether. Transfer each lot of ether as it separates, into a small silica crucible on a water bath. (2) Dissolve the residue when quite dry in a minimum amount of anhydrous ether. (3) The ether solution is now transferred drop by drop on a warm microscopic slide so that the residue left by its evaporation is spread over a minimal area. (4) Put on a cover slip and add just enough of Christensen's reagent (Iodine, 1 gm.; 50 per cent. HI, 1 gm.; concentrated H_2SO_4 , 0.8 gm.; 70 per cent. alcohol, 50 gm.) to fill up about $\frac{1}{3}$ of the enclosed space and by gentle pressure bring it in contact with the residue left by the ether. If quinine be present blackening will be visible to the naked eye. Examine microscopically when golden green tablets or leaflet like crystals will be seen, and observe effects of rotating a Nicol's prism over the eyepiece on the illumination of the crystals, and they should rotate the light like tourmaline. The alkaloids quinidine, cinchonine and cinchonidine give crystals of similar activity and 0.0005 mgm. of quinine can be detected in 40 c.cm. of water.

4. *Tanret-Mayer Test.* The reagent is prepared by dissolving 1.45 gm. of HgCl_2 in 80 c.cm. of distilled water and 5 gm. of KI in 20 c.cm. of

distilled water and mixing them in a 100 c.cm. measuring flask. The HgCl_2 solution is poured into the KI solution agitating all the time, water is added to make it up to 100 c.cm. This reagent precipitates all alkaloids and gives a good rough test for the presence of quinine in urine. The urine is acidified and boiled to free it from albumin and is filtered. Five c.cm. of this is taken in a test tube and Tanret Mayer Reagent is added. A precipitate shows the presence of the alkaloid. If there is no distinct turbidity the patient has not taken quinine. Mann suggests taking 50 c.cm. of urine and adding 2.5 c.cm. of lead acetate solution (lead acetate 25 gm., glacial acetic acid 2.5 c.cm., water to 100 c.cm.); mix thoroughly and add 2.5 c.cm. of saturated aqueous solution of ammonium sulphate; filter till a clear lead-free filtrate is obtained. Receive a drop of filtrate on a paper moistened with a sulphide to test for lead and also boil to test for albumin. To 10 c.cm. of this add 0.5 c.cm. of Mayer's reagent. An opalescence or turbidity indicates the presence of quinine. Very slight traces of quinine may only show after the mixture has stood for 10 to 15 minutes.

Another simple test for quinine in urine is to take 10 c.cm. of lead-free urine as obtained in the above test and adding to it 6 drops of 1.0 per cent. solution of picric acid. A cloud forms if quinine is present, disappearing on heating and reappearing on cooling. A precipitate due to albumin increases on heating and falls on standing. The test responds to 3 grains of quinine taken an hour before examination.

Quinine mixtures used in dispensaries in this country are not infrequently below strength. Two methods for testing the approximate quantity have been described.

Sinton's method: Prepare Tanret's modification of Mayer's reagent. Heat a portion of the quinine solution to exclude the presence of albumin. If albumin is present it must be removed before testing the solution. Acidify with acetic acid, boil, and filter the solution. Take 4 c.cm. of the quinine solution freed from albumin, place it in a flask, and dilute with distilled water to 250 c.cm. In one of the special spare tubes provided with each set of Brown's opacity tubes for vaccine preparation place one volume of the quinine solution. Add to it one volume of Tanret's reagent and shake well. The solution will become more or less opaque.

Match the opacity with Brown's tubes. This is done by taking the tube under test in turn with each of the standard opacity tubes, and laying the tubes side by side in a good light, upon some clearly printed book. The lighting must be equal in the two cases. The opacity of the two suspensions can then be readily compared by rolling the tubes from side to side, and raising them slightly from the surface of the print. Brown's tubes are numbered from 1 to 10, and Sinton states that these numbers may be taken to represent the number of grains per ounce in the quinine solution under test. A quinine solution

containing 10 grains of quinine to the ounce should show an opacity of 10

As a control to the test, a fresh solution of 10 grains of quinine to the ounce should be made up and tested at the same time. If the solution is weaker than 10 grains to the ounce, solutions of different strengths can be prepared from the control solution by diluting it, and the tests repeated until a match is obtained.

5. *Megaw, Ghosh and Chatterjee method:*

Requirements:—(1) A supply of long narrow test tubes of equal calibre (5 to 7 mm diameter if possible). Wider tubes may be used but they would necessitate the use of larger amounts of the solutions. Calibrated and graduated tubes such as centrifuge tubes are preferable if available.

(2) **Reagent:—**Twenty gm. of Merck's pure phosphotungstic acid is dissolved in 100 c.cm. of 12.5 per cent. sulphuric acid. The dilute H_2SO_4 is made by mixing 5 c.cm. of B.P. concentrated sulphuric acid of 1.84 specific gravity with 50 c.cm. water, cooling, and making up to 70 c.cm. with more water.

(3) The stock solution which is to be tested. (This should be diluted if it contains more than 20 grains of the alkaloid in each ounce; in this case, the control solution should be diluted in the same proportion).

(4) A freshly prepared solution should be made up in one's presence, using the same amount of quinine or cinchona febrifuge as is supposed to be present in the stock solution, the powders which are in stock in the dispensaries being employed. In cases of doubt as to the purity of the powdered alkaloid in stock, another solution should be made using powders of known purity. This will serve as a control of the quality of the stock powders.

Method —In one tube take 1 c.cm. (or one part) of the stock solution, in another tube take exactly the same amount of the freshly prepared solution (a third tube may be used for the solution made from alkaloids of known purity). Measurement by a pipette is desirable but with reasonable care equal quantities can be measured.

To each of the tubes add 2 c.cm. (or 2 parts) of the reagent and 1 c.cm. (or 1 part) of water. Mix thoroughly by rolling the tubes between the hands for about a minute keeping them in a vertical position. Do not stir or shake the solutions. Allow the precipitates to settle for 2 or 3 hours and compare their heights. Any great variations will indicate the necessity for an accurate quantitative examination of the stock mixture.

If centrifuge tubes and a centrifuge are available the examination can be completed in a few minutes, but the test has been specially worked out so that it can easily be carried out with the simplest possible equipment.

The test solution ready made up can be obtained from any reliable chemist by supplying him with the formula. It keeps indefinitely. It is essential that the tubes employed should be of equal calibre and the quantity of the quinine solution in each tube must be the same. The total volume should be such as to give a 5 per cent. solution of sulphuric acid, at which the reagent acts best. No claim of great accuracy is made for this test, but it will be found useful as a rough check of the strength of dispensary solutions. As already stated, it can also be used to detect any serious deficiencies in the purity of the powders from which the stock mixtures are made. Messrs. Boots Pure Drug Co., Ltd., have prepared a handy 'Quin-Iodide Test Outfit' based on this method.

Hydroquinine. This compound is commonly present in the commercial sulphate of quinine from 1 to 2 per cent. It is best prepared by re-crystallising commercial quinine from hot water and treating the mother liquor with potassium permanganate. It forms two series of salts—the neutral and the acid salts. The dosage is the same as for quinine.

Cinchonidine is an isomeride of cinchonine, and occurs especially in the bark of *C. succirubra*, *C. officinalis*, *C. lucujensis*, and *C. lancifolia*. The sulphate has largely been used to adulterate quinine as it is much cheaper.

Preparation. Cinchonidine is isolated from the liquid strained off from quinine. It is separated as a tartrate, cinchonidine tartrate being only slightly soluble in water.

Properties. Cinchonidine behaves as a diacidic base and yields two series of salts. The neutral sulphate is sparingly soluble but the acid sulphate is easily soluble in water. Neutral and acid hydrochlorides are also soluble.

Tests. Cinchonidine differs from quinine and quinidine in that it does not give the thalleioquin reaction and is not fluorescent in dilute sulphuric acid solutions, and from cinchonine in being more soluble in ether, in the sparing solubility of its tartrate and in being laevorotatory.

Dose. It has largely been employed in the treatment of malaria unknowingly as it is commonly used to adulterate quinine. It is less toxic than quinine and 10 to 15 grains may be given two or three times a day.

Hydrocinchonidine is the hydro-compound of cinchonidine and occurs in most varieties of cinchona bark especially the *C. rosulenta*, and *C. lancifolia*. It may be prepared from commercial cinchonidine sulphate by fractional precipitation. The dose is the same as that of cinchonidine.

Quinidine. This isomeride of quinine is contained in small quantities in most cinchona barks, but especially in *C. pitayensis*, *C. amygdalifolia* and *C. calisaya*.

Preparation. The mother liquor after the separation of quinine sulphate is treated with caustic soda, which precipitates the remaining alkaloids. These are now extracted with ether. The ethereal residue is dissolved in dilute sulphuric acid, neutralised exactly with ammonia, and sodium potassium tartrate is added which precipitates the cinchonidine. The filtrate is now treated with KI solution which precipitates the quinidine as hydriodide. From this it is removed and recrystallised from boiling alcohol.

Properties. Quinidine is alkaline in solution and behaves as diacidic base forming two series of salts. The neutral and acid sulphates are soluble in water. The acid hydrochloride is sparingly soluble. The melting point of the base is 171.5°C and the optical rotation is $+236.7^{\circ}$ in 97 per cent. alcohol.

Tests. It is fluorescent in dilute sulphuric acid and gives the thalleioquin test. It differs from quinine in being dextrorotatory, possessing a sparingly soluble hydriodide (1 in 1250 at 12°C) and a neutral sulphate fairly soluble. The tartrate is soluble and this fact is utilised in the separation of cinchonidine.

Dose. It has a much more powerful action on the heart than quinine, 5 to $7\frac{1}{2}$ grains is the usual dose given two or three times a day orally.

Hydroquinidine is the hydrocompound of quinidine and occurs in commercial quinidine.

Cinchonine occurs constantly in cinchona and cuprea barks, but the amount present is small and shows great variations. One of the best sources is *Cinchona micrantha* bark.

Preparation. After quinine sulphate has been separated, the mother liquor is treated with caustic soda solution, when the remaining alkaloids come down as a precipitate. The precipitate is extracted with ether and the insoluble residue is boiled with successive small quantities of alcohol, and on cooling cinchonine crystallises out. The crude alkaloid is exactly neutralised with dilute sulphuric acid and the sulphate recrystallised from boiling water.

Properties. Cinchonine behaves as a diacidic base and gives two series of neutral and acid salts. The melting point of the base is 264° and the optical rotation $+229^{\circ}$ in dry alcohol.

Tests. Cinchonine differs from quinine and quinidine in that it does not give the thalleioquin reaction and is not fluorescent in dilute sulphuric acid, and from cinchonidine in that it is sparingly soluble in ether and is dextrorotatory.

Dose. It is one of the most toxic of cinchona alkaloids. More than 10 gr. twice a day, is not generally tolerated.

Hydrocinchonine is the hydro-derivative of cinchonine and occurs in most varieties of cinchona bark and is a constant constituent of commercial cinchonine.

B. Amorphous alkaloids.

Quinoidine is the name given to the combined amorphous alkaloids which remain in the mother liquor after the crystalline alkaloids are removed. Acton (1920), Fletcher (1923) and others found them too poisonous to be used in therapeutics, while Waters (1916) and Prain (1924) consider them to be entirely non-toxic and as effective against malaria as quinine. It is held that these substances being amorphous are more readily absorbed and are of greater value than quinine salts. Benign tertian required 9 to 13½ grains of quinoidine to stop fever, while malignant tertian required 10 to 16 gr. and quartan on an average 22 to 24 gr. *Laverain tablets* contain 2 gr. of quinoidine, ½ gr. of ammonium picrate and 1/100 gr. of arsenious acid; dose 6 to 12 tablets in the day. The preparation is said to be prompt in reducing fever. *Esanofele* is a similar preparation.

Fletcher (1924) reinvestigated the subject and found they had no action whatever against malaria when given in 5 grain doses twice a day. Ten grains twice a day were effective but toxic, the chief symptoms being vomiting and diarrhoea. Both *cinchona febrifuge* and *quinetum* contain large quantities of cinchona alkaloids.

Cupreæ cortex or **Cuprea bark** is obtained from *Remijia pedunculata* and other species. It contains quinine and an allied alkaloid, cupreine. A number of derivatives of the aliphatic series have also been prepared. It will therefore be useful to mention some of these preparations in this connection.

Methyl hydrocupreine hydrochloride is also known as hydroquinine hydrochloride. Dose 4 to 12 gr. (0.25 to 0.8 gm.) for adults in malaria. In whooping cough in children it is given in 1 to 5 or 6 gr. intramuscularly, according to age.

Ethyl hydrocupreine or **optochin**, is a white amorphous powder with a bitter taste, almost insoluble in water, soluble in alcohol, ether, chloroform and dilute acids. Dose 3 to 4 gr. (0.2 to 0.25 gm.). It is used in pneumonia. **Ethyl hydrocupreine hydrochloride** is given in the same dose as the base and it is soluble in water.

Iso-amyl hydrocupreine. This derivative according to Dixon (1920) is 10 to 20 times more powerful than quinine in the destruction of protozoa, 0.1 per cent. solution acts as a germicide and as a local anæsthetic.

Iso-octyl hydrocupreine or **vuzin** is said to have a specific action on *C. diphtheria* and enough can be given in medicinal doses to clear this organism from the blood.

CHAPTER XXV

OTHER ANTIMALARIAL REMEDIES

PLASMOQUIN

Owing to the high price of quinine, its bitter taste, and its failure to remove crescents from the blood, attempts have been made from time to time to find stronger and better substitutes for it. These researches led to the synthesis of various antipyretic drugs, such as antipyrin (1884), phenacetin (1886), etc. In 1926, Professor Schulemann and his colleagues chose methylene blue as the starting point for investigation and they prepared a large number of compounds. One of these as tested by Roehl was found to be particularly effective against bird malaria; this was an amino-quinoline in which a basic aliphatic radicle was united to a quinoline nucleus by a connecting link of nitrogen. The structure of this drug has not been wholly disclosed, but according to Horlein (1926), the compound is *n*-diethyl-amino-isopentyl-8-amino-6-methoxy-quinoline, thus differing from quinine principally in the absence of quinuclidine with two intermediate CH_2 radicals. Plasmoquin while not a derivative of quinine is genetically related to that alkaloid. The first announcement concerning it was made in September, 1926. It has also been called 'plasmochin' and later in English-speaking countries it was called plasmoquin or plasmoquine. 'Beprochin' is a substance of a similar nature. Both these substances are very expensive. *Fourneau 664* is another compound allied to plasmoquin. *Dimeplasmin* is a synthetic remedy of the plasmoquin group, prepared by the manufacturers of plasmoquin. A large amount of experimental work was done at first on bird malaria by Roehl (1926). It had been shown that apart from arsenicals, the substances effective against malaria in man are effective against bird malaria also. This process was reversed in the case of this drug and it was found that a drug useful in bird malaria was found to be beneficial in malaria in man. Roehl found that plasmoquin

had a definite destructive action on the plasmodium in the birds and was nearly 60 times stronger and more effective than quinine. One c.cm. of 1 in 50,000 solution of plasmoquin given daily for 6 days delays development of plasmodium in canaries while the same quantity of 1 in 800 solution will be necessary in man. These results were confirmed in bird malaria by Hegner and Manwell (1927). Later, it was found that *Hæmoproteus* may be temporarily removed from the peripheral blood of thrushes; in pigeons plasmoquin removes the gametes of *Hæmoproteus* from the peripheral blood stream, though they return again after a few days. Plasmoquin destroys the gametocytes, but not the schizonts.

Pharmacological action. On non-pathogenic protozoa such as paramœcia, plasmoquin like quinine has a lethal action but in double the concentration of the latter drug. In the dark however plasmoquin is more effective than quinine as light seems to activate the latter drug. When the two drugs are mixed they appear to reinforce each other's action and the toxic action on paramœcia is intensified.

Circulation. Eichholtz (1927) studied the action of this drug on the circulation. In cats, doses of 2.5 to 5 mgm. per kilo. of body weight caused formation of methaemoglobin. In cats, dogs and rabbits, intravenous injections produced cardiac incoordination. In large doses (1 to 3 mgm. per kilo. of the body weight) the drug increases the refractory period of the ventricles and heart-block may be produced. The heart becomes irregular, there may be duplication or suppression of the systole. With higher doses the heart is depressed and the blood pressure falls. Adrenalin brought about normal rhythm in the heart poisoned with plasmoquin and produced the usual rise of blood pressure. Like quinine it does not decrease the number of white blood corpuscles but in a few cases actual increase was noticed in man. Quinine in certain doses is said to prevent the toxic effect produced on the heart and that is the reason why plasmoquin and quinine are combined in the form of plasmoquin compound tablets. This however seems to be doubtful. Leucocytosis sometimes follows the administration of plasmoquin, many young undifferentiated leucocytes being present. It is therefore preferred in malaria complicated with pneumonia.

Uterus. Chopra and his co-workers (1938) have shown that plasmoquin in therapeutic doses has no action on the uterus. In large doses it produces contractions of the isolated uteri of cats and guinea pigs. That plasmoquin prevents the stimulant effect of quinine on the uterine contractions is not borne out by experiments. When proportionately equal doses are employed the action of plasmoquin in the cat and man is similar.

Central nervous system. Plasmoquin is poisonous to the central nervous system.

Excretion. The fate of plasmoquin in the body is not known. That it is partially excreted in the urine there is little doubt. Its presence can be actually detected in the urine. To detect plasmoquin in urine take 200—300 c.cm. of the urine, add 20 c.cm. of 50 per cent. liquor potassae and centrifuge three times, each time with the addition of 30 c.cm. of pure ether. Take out the ethereal solution, and it turbid add a few drops of alcohol, filter and wash twice with 10 c.cm. of water containing two drops of NaOH. Shake well, allow to settle and draw out the aqueous layer. To the ethereal solution add 6 c.cm. of 2 per cent. acetic acid, and shake well, take off the acetic acid solution containing plasmoquin and heat on a water bath for some time to remove the residual ether. Add 3 c.cm. of pure glacial acetic acid and about 0.05 gm. of chloranil (tetrachlor-benzoquinone) and lightly boil the solution. An intensive blue colour reaction develops which shows the presence of plasmoquin.

Toxicity. The lethal dose in rabbits is 3.5 mgm. per kilo. body weight intravenously, 20 mgm. subcutaneously and 225 mgm. by the mouth. In the cat it is more toxic, 5 mgm. intravenously is fatal while the same amount will kill when given subcutaneously and 7.5 mgm. by the mouth. Cats recover more quickly than rabbits after sublethal doses. Death occurs with symptoms of dyspnoea, asphyxia, bradycardia and arrhythmia, with methaemoglobinaemia. It has been shown that plasmoquin forms methaemoglobin with the blood of the sheep, ox, horse, cat, rabbit, dog and man *in vitro*. In man one-third of the oxygen capacity of the blood may be lost, as the result of this conversion. In acute poisoning the symptoms appear in the following order. First there is paralysis of the vasomotor system with fall of blood pressure, slowing and then complete cessation of respiration; the cardiac rhythm remain undisturbed till the end. Lethal and therapeutic doses in man are not widely separated.

Effectiveness Against Malaria

The drug was first tried on man by Sioli (1926) who cured several patients artificially infected with malaria in the course of treatment for general paralysis. Muhlen and Fischer (1927) tried the drug in patients suffering from malaria. In a series of 172 cases he found that 0.08 to 0.1 gm. per day was an effective dose in tertian and quartan malaria. The drug was later tried in most of the malarious countries in Europe, the main results of these observations being that plasmoquin in doses of 0.06 gm. per day given daily for one week, and for 3 days in the week for five weeks was effective in curing malaria. This was

the method recommended by the manufacturers. Sinton (1928) gave the drug daily for 28 consecutive days and found this method more effective though more toxic. The conclusions arrived at are that the destructive action of plasmoquin is restricted to infections by *P. vivax* (benign tertian) in all phases, and that while it has no action on the schizonts of *P. falciparum* (malignant tertian) it has a definite action on the crescentic gametocytes of this organism.

Action in benign tertian and quartan malaria. Both benign tertian and quartan parasites disappear from the blood more rapidly than the sub-tertian, and cure is said to be more readily effected in these infections than with quinine. After doses of 0.01 gm., 4 or 5 times a day or 0.06 gm. daily, the fever usually disappears from the first to the third day of treatment. The parasites may disappear as early as on the 2nd day or as late as on the 7th day of treatment. Relapses do not occur so frequently as with quinine. Sinton (1928), who watched his cases for long periods, found that 30 per cent. of patients suffering from benign tertian infections relapsed after intermittent treatment with plasmoquin and 23 per cent. relapsed after ordinary treatment with quinine. Immediate results however obtained in acute attacks after treatment with this drug were no better than those obtained with cinchona alkaloids. In quartan fever similar results were obtained but the parasites remained somewhat longer in the peripheral blood. Although the number of cases was small, no relapses were reported in quartan fever. Plasmoquin and quinine together, are believed by many authorities to be more effective in destroying the sexual forms of benign tertian and quartan parasites, than quinine alone.

Action in subtertian malaria. As regards subtertian infections, plasmoquin has no action at all upon the schizogony cycle, and the parasites multiply unchecked. On the other hand it has the unique and remarkable property of completely destroying the gametocytes or 'crescents',—a property which is not possessed by either quinine or atebirin. This effect on the crescents can be studied microscopically; on the first day after plasmoquin administration the crescents are seen to be degenerat-

ing and stain badly ; on the second day they are so degenerated as to be hardly recognisable ; on the third day none are found. Hence in subtertian malaria the administration of plasmoquin has to be supplemented, either with quinine or atabrin. If a patient suffering from subtertian malaria be treated only with quinine or atabrin and is clinically cured, to turn him out of hospital at this stage with his blood loaded with crescents, fully infective to mosquitoes, is a crime against public health, since he may infect hundreds of mosquitoes in his home with malaria. In all cases of subtertian malaria, after the patient has been cured with quinine or atabrin, a short course of plasmoquin—0.01 gm. twice daily for three days—should be given. This will ensure that the patient is not a danger to the countryside when he returns to his home.

Effects on the gametocytes. Plasmoquin has a definite destructive action upon the gametocytes and removes the crescents from the peripheral blood in a very short time. None of the cinchona alkaloids have any effect on the crescents, nor do the arsenicals or the aniline dyes affect them adversely. Even small doses (0.02 to 0.04 gm.) of the drug daily for three days are said to render the peripheral blood non-infective to anopheline mosquitoes; a single dose may render crescent-containing blood non-infective for three days. These facts are of great importance from the point of view of the transmission of malaria from one person to another.

Fletcher (1927) said that plasmoquin has the property of destroying the gametocytes of malignant tertian infection and this unique attribute holds out a hope for eradicating malaria by mass treatment. Manson-Bahr (1928) states that within 36 hours of the administration of 0.08 gm. plasmoquin and 1 gm. quinine, crescents are deformed and in 60 hours they are completely disintegrated. The average time and quantity required for disappearance of the crescents from the blood were 4 days and 0.3 gm. respectively. Mollow (1928) described the direct toxic effect of the drug on the crescents and the changes which take place in these bodies. Definite signs of degeneration were noted in crescents within 36 hours of the commencement of plasmoquin medication, and 24 hours later the crescents were

entirely disintegrated. According to Fischer and Weise (1927) the daily dose of the drug, to remove the crescents from the blood, is 0.02 to 0.03 gm. ($\frac{1}{3}$ to $\frac{1}{2}$ gr.).

Practical trials of antigametocyte action of plasmoquin have been made by Clemesha (1933). Although the trials were on a small scale, the results show that it is possible to control the spread of malaria by careful antigametocyte work. Two doses of quino-plasmine a week usually effect a great reduction of parasites (trophozoites or schizonts) in the peripheral circulation. Malignant tertian and benign tertian gametocytes are never found if the dose is taken regularly. Quartan parasites are less acted upon by plasmoquin than other two varieties. Two doses of quino-plasmine a week cause the attack, even of malignant tertian, to be mild in character. The objection to this procedure is the trouble and expense involved; but the cost is much less than that occasioned by a severe outbreak of malaria.

Plasmoquin compound. The insufficient action of plasmoquin on the ring forms and schizonts of subtertian malaria led to the use of a combination of plasmoquin and quinine sulphate. This is given in tablet form, each tablet containing 0.005 gm. of plasmoquin and 0.0625 gm. of quinine sulphate, but the quantities of both drugs are very small and tablets containing double the strength, *i.e.*, 0.01 gm. and 0.125 gm. respectively are more convenient. In this proportion the toxic effects of both the drugs are minimised. It is desirable that the dose of 0.06 gm. of plasmoquin per day should not be exceeded, as otherwise toxic symptoms are produced. A much smaller amount than this may effect a cure and the presence of small quantities of quinine, which otherwise would not be effective, gives better results when combined with plasmoquin.

In subtertian malaria treated with plasmoquin compound, the fever usually disappears after 2 to 3 days, and the parasites between the 2nd and the 7th day. Relapses do occur but they are not so frequent as with quinine alone. This is not borne out by Sinton's observations and in a large series of 554 cases treated by Olivier and Hulshoff in Java no relapses occurred after treatment with plasmoquin compound.

Muhlens (1927) and Hasselmann (1929) advised 6 tablets of plasmoquin compound daily in divided doses, each tablet containing 0.01 gm. plasmoquin and 0.125 gm. quinine.

Macphail (1930) in the Fruit Company hospital in Guatemala gave a routine treatment of three tablets of plasmoquin compound daily for six days, together with 15 grains of quinine twice daily. No toxic symptoms resulted in 20,000 cases treated.

Quinoplasmine. This is the commercial name for tablets of plasmoquin 0.01 gm. and quinine 0.3 gm. Four tablets are given daily for 4 to 21 days. With this treatment 100 per cent. of definite cures in quartan malaria and 4 per cent. relapses in benign tertian malaria have been obtained.

Other effects. With the subsidence of fever the blood condition is improved, the anæmia disappears and the hæmoglobin content is increased. A marked decrease in the size of the spleen has been noted by a number of other observers. Sinton on the other hand found that the reduction was no more marked than with ordinary quinine treatment, but this was probably due to the fact that most of his cases were those of chronic relapsing malaria.

In cases of malaria complicated with ear diseases (*e.g.*, internal and middle ear disease, deafness) and also in menorrhagia, where quinine is not indicated, plasmoquin is specially suitable. The drug is well borne in pregnancy and is not affected by the presence of intercurrent diseases such as tuberculosis of the lungs, nephritis, valvular disease of the heart, pneumonia, jaundice, typhoid, etc. Children and even infants bear plasmoquin very well and further it has the advantage of being tasteless. It has also been used in the treatment of blackwater fever in place of quinine, but in view of the dangerous and even lethal effects that are sometimes noticed with the drug, plasmoquin should not be used in such cases; atebryn is better as a substitute for quinine.

Dosage. The maximum dosage without producing toxic effects is 0.03 gm. per day. According to Muhlens the dosage for quartan and tertian malaria is 6 plasmoquin compound tablets daily each containing 0.01 gm. of plasmoquin and 0.125 gm. of quinine divided into 2 or 3 doses. This means 0.06 gm. of plasmoquin and 0.75 gm. of quinine per day; 0.02 gm. may be given 3 times a day for a week. The fever disappears in 1 to 2 days and the parasites in 5 or 6 days. The amount of quinine to be given daily in combination with

plasmoquin depends on clinical symptoms. In chronic cases with acute symptoms 1.0 gm. may suffice. In acute cases it may be necessary to give larger doses. In ambulatory cases not under daily supervision not more than 0.04 gm. of plasmoquin should be given daily for periods not exceeding six days. Manifold (1931) adopted a standard treatment of one tablet of plasmoquin 0.02 gm. and 10 grains of quinine morning and evening. In malignant tertian cases the drugs were continued for 21 days. It has recently been claimed that plasmoquin in 0.02 gm. doses effectively prevents mosquito-borne malaria infection; quinine lacks this remarkable property.

The patient as a rule does not develop tolerance to this drug. Interrupted treatment as a rule is more satisfactory, the drug being given twice a week for 4 to 6 weeks.

Children tolerate plasmoquin very well and it has the advantage of being tasteless. Infants 6 months old can be given 0.005 gm. twice daily without ill effects.

Toxic effects. Like most of the highly efficacious synthetic remedies plasmoquin is a toxic drug. The appearance of untoward effects depends not only on the dosage given but on the temperament and susceptibility of the patient. Nervous patients are particularly liable to suffer. Cyanosis and epigastric pains were observed very early after trials in man, and they are universally present though they vary a great deal in their intensity in different individuals. Slight jaundice, cyanosis and abdominal pains are by no means rare. The appearance of cyanosis ought to serve as a warning to reduce the dose or to stop the drug. Cyanosis has appeared after 0.08 gm. In mild cases there may only be cyanosis of the fingers, toes and lips but the face and the whole body may be involved. According to some it rapidly disappears on subsequent treatment with quinine, plasmoquin and quinine being mutually antagonistic in this respect. Abdominal pains and gastric disturbances are common when the drug is given on an empty stomach in large doses. Some believe they are due to rapid decrease in the size of the spleen. Muhlen and others state that these pains do not appear if the drug is given after meals. Sliwensky (1927) gave a whole day's dose amounting to 0.06

to 0.08 gm. all at once after the morning meal and never observed any gastric disturbances. Others have reported sudden attacks of pain which became very alarming and in many cases a course of treatment cannot be finished without toxic symptoms.

Intoxication symptoms as a rule have not been recorded unless the dose reaches 0.18 gm. The face is livid grey, but there is no dyspnoea nor undue distress. The patient complains of headache, dizziness, curious clammy sweats, abdominal pains, vomiting and a sensation of bruising over the lower ribs. The pain may be specially marked in the region of the liver, and central necrosis of liver lobules has been observed. In some cases the symptoms resemble an attack of cholera,—subnormal temperature, vomiting, diarrhoea and cyanosis being present. Cyanosis may be associated with haemoglobiuria, involvement of the liver and intestinal symptoms. The blood turns chocolate coloured and methaemoglobinaemia and methaemoglobinuria occur. Urobilinogen appears in the urine simultaneously with the administration of the drug and persists for several days. The patient turns drowsy and becomes comatose. Pallor with marked drop of erythrocytes and haemoglobin count, exhaustion, and yellowness of the skin, are some of the symptoms. Haemoglobin falls to 30 per cent. the leucocyte count rises to 24,000 per c.mm., and the oxygen capacity of the blood is decreased. In one case symptoms appeared after 0.4 gm. of plasmoquin in daily doses of 0.12 gm. Methaemoglobin appeared in the urine 24 hours after cyanosis and was accompanied by albumin and casts. The picture resembled that of mild blackwater fever. Jaundice may occur. Cyanosis may last for 24 hours after the drug is stopped but rarely may last as long as seven days. The serum becomes brownish with a strong direct bilirubin reaction and with urobilin strongly positive. There is a good deal of destruction of red corpuscles the number falling to half the normal amount. Many explanations have been given for the occurrence of cyanosis. It has been said to be due to disturbance of the heart rhythm, but most authorities believe it to be due to the formation of

methaemoglobin, which has been detected in the urine and in the serum.

There is no direct connection between the amount of the drug given and the quantitative degree of change in the blood, although the most violent symptoms are only seen after large doses. The number of erythrocytes present in the blood appears to have a great influence on the toxic symptoms. The greater the anaemia, the quicker and more violently methaemoglobin is formed, and the deeper is the cyanosis. It follows therefore that patients suffering from secondary anaemia should be given only small doses of plasmoquin. The temperature of the individual is also a determining factor, the higher the temperature the more quickly is methaemoglobin formed. In certain patients cyanosis occurs even with small doses of the drug. The quinoline chain apparently is not responsible for the formation of methaemoglobin, but probably the alkamino group is really responsible and this occurs in such methaemoglobin-forming drugs as acetanilide and phenacetin. Cyanosis generally appears on the 5th or 6th day of the treatment.

A direct haemolytic effect on the part of this drug is disclaimed and it is believed that it acts on the reticulo-endothelial cells (Kupfer's star-cells) of the liver, whereby its detoxicating properties are decreased.

On account of the frequency of toxic symptoms, which are sometimes of an alarming nature, plasmoquin should only be used under hospital conditions. The drug is not as suitable for mass treatment as is quinine.

Prevention and treatment of toxic effects. The poisoning can be prevented by careful dosage, taking into consideration the body weight and general condition of the patient. A few drachms of glucose given daily, either in powder or liquid form, may prevent the onset of toxic symptoms. The drug should be given an hour and a half after a light meal. The bowels should be kept open. When symptoms have supervened the drug should be stopped and the patient strictly confined to bed and given copious alkaline drinks. Stimulants and mild non-irritating diuretics are indicated. In

severe cases of methaemoglobinaemia and methaemoglobinuria the patient may be benefited by transfusion of blood.

Prophylactic value. Owing to the action of plasmoquin on the gametocytes, the question of its utility in malaria epidemics is worth considering. Experiments carried out in Java showed that plasmoquin had a well marked prophylactic value, especially in benign tertian malaria. In Bulgaria trials on a small scale showed that administration of plasmoquin compound to gametocyte-carriers in doses of 0.07 to 0.08 gm. daily for six days kept them parasite-free for 4 months. It is suggested that if this procedure can be carried out in malaria-stricken areas 2 or 3 weeks before the anopheles period, the number of fresh infections could be considerably reduced. Clemesha (1933) obtained good results with two doses of quinoplasmine a week.

Plasmoquin in doses of 0.08 gm. on the day before infection, the day of infection, and the day after, and subsequently in doses of 0.06 gm. for the following five days is said to be a true causal prophylactic. Such doses, however, are liable to produce toxic effects. A daily dose of 0.04 gm. on the day before infection, the day of infection and for eight days after infection will always prevent the onset of a malarial attack within the usual incubation period, but will not prevent the person having a latent infection which may become manifest at a later period, usually six to ten months after infection. With smaller doses failures are more frequent. Some workers have found that daily doses of 0.02 gm. of plasmoquin prevented to a great extent fresh infection, but not when doses were given only three times weekly. Such doses even when given daily are not sufficient to kill all sporozoites injected, though they keep the malarial manifestations below the febrile threshold while the drug is being administered. This is evident from the fact that many persons develop clinical malaria, shortly after the cessation of the drug. It will be seen, therefore, that plasmoquin is not adoptable for prophylactic purposes in malaria.

Plasmoquin in pregnancy. In therapeutic doses plasmoquin has no effect on the uterine contractions and it is considered to be a safer drug than quinine in malaria in pregnancy.

Mode of action of plasmoquin. The exact manner in which plasmoquin produces its destructive action on the malarial parasites is not understood. It has been suggested that the action of plasmoquin in malaria may be at least partly due to its

capacity of converting haemoglobin into methaemoglobin. This would lead to the lysis of the red blood cell and consequent destruction of the parasite.

Plasmoquin in blackwater fever. Plasmoquin has been employed in cases of quinine idiosyncrasy and blackwater fever and it appears to be well borne. The dosage was very slowly increased, *i.e.*, beginning with 0.01 gm. per day and increasing gradually to 0.06. It causes disappearance of malarial parasites from the blood and haemoglobinuria disappears in 24 hours. Administration of quinine may again produce haemoglobin in the urine in these cases. Cases of malaria with idiosyncrasy to quinine have been successfully treated with plasmoquin.

Conclusions. Plasmoquin is a toxic drug, and the hope that it will replace the cinchona alkaloids in the treatment of malarial fever has not been fulfilled. On account of its toxic effects it has to be given under strict medical supervision. Its employment is indicated where there is idiosyncrasy to quinine, and in pregnancy where there is risk of abortion from the use of quinine. A safe dose is 0.06 gm. per day as it is therapeutically effective and less likely to produce toxic effects. Children tolerate it well and in malaria of infants it is very useful. A combination of plasmoquin with quinine, is equal if not superior to quinine alone. Its action in rendering gametocytes non-infective to mosquitoes is of very great importance, and with plasmoquin compound there is possibility of sterilising the carriers. Plasmoquin by itself should never be used in the treatment of malarial fevers. For the treatment of benign tertian the combination with quinine (plasmoquin-compound) is most suitable, it having been found that a small dose is quite sufficient if supplemented with quinine. In malignant tertian it is not curative, but its action on the gametocytes has led to its employment as an antigametocyte, a measure which has been shown to be a practical form of malaria control.

Preparations.

Plasmoquin is issued in tablets in three varieties:—

Plasmoquin simplex 0.01 and 0.02 gm. Dose 1 to 3 tablets daily.

Plasmoquin compound containing plasmoquin 0.01 gm. and quinine 0.125 gm.

Quinoplasmine or **quino-plasmoquin** containing plasmoquin 0.01 gm. and quinine 0.3 gm.

ATEBRIN

Six years ago the introduction of plasmoquin marked the inauguration of the use of synthetic compounds in the treatment of malaria. Plasmoquin, however, has not entirely replaced quinine. Its action on the parasites is different; plasmoquin destroys the sexual forms of *P. falciparum*, thereby interrupting the transmission cycle, but it has no action on the asexual forms. This limitation of plasmoquin indicated that further research was necessary, and as a result the makers of plasmoquin recently announced the introduction of a new compound called *Atebrin*. The product, first called 'erion' or 'plasmoquin E', is the dihydrochloride of an alkylamino-acridine derivative; it is a yellow powder having a bitter taste, soluble in water 1 : 14 forming a neutral fluorescent solution. Both drugs have been evolved by using the structural formula of methylene blue as a starting point.

Pharmacology. Administered by the mouth, atebrin is quickly absorbed from the small intestine and passes into the blood stream whence it is slowly excreted unchanged by the kidneys and the biliary tract. It is fairly well tolerated but when large doses are administered in animals, diarrhoea and reflex salivation occur. Frequent vomiting is also noticed. The diarrhoea however usually subsides within 24 hours. If the drug is injected intravenously into rabbits under anaesthesia, a fall of blood pressure is obtained within 1—2 minutes. This fall is not due to any direct action on the cardiac musculature, but is probably due to a transient dilatation of the capillaries in the splanchnic and peripheral areas. The plain muscles of the small and large intestines and the uterus are not affected in any way after intravenous injections in anaesthetised animals. A slight reduction of temperature ranging up to 1° C. has however been obtained in rabbits with induced fever. This reduction in temperature lasts for about 12 hours.

Fate in the body and excretion. Atebrin is eliminated slowly and may be found in the urine many days after completion of a course. The urine should be examined daily during treatment, as its absence indi-

cates possible accumulation in the system which may give rise to a yellow colouration. The drug is mostly excreted by the kidneys and its presence can be roughly detected in the urine by production of the characteristic yellow colour on addition of an acid. The test suggested by the makers is to extract the alkalinised urine with ether, and dissolve the residue resulting from the evaporation of ether extract in strong sulphuric acid, when a yellow colour appears. This latter test is more accurate, and the author actually uses a modification of it. The urine is first treated with lead acetate to remove all other matter and the lead is removed from the filtrate by the addition of ammonium sulphate. The filtrate is then extracted with ether and tested with acid in the ordinary way. The drug appears in the urine on the second day after administration and can be detected up to 15 or 20 days or even longer. The excretion is not regular and may stop for a day or two and then reappear. The author's observations on Indian patients confirm the view that there is some tendency towards accumulation of the drug in the body. Atebrin undoubtedly persists in the body for a much longer period than quinine or plasmoquin. If excretion is hindered there is a tendency for the appearance of the dye in the skin which assumes a yellowish tinge.

Toxicity. Cats tolerate oral doses of 0.05 gm. per kilo. body weight without any reaction. After administering 0.07 gm. the animals show symptoms of gastro-intestinal irritation. On an average 0.1 gm. per kilo. by the mouth is the minimum lethal dose, the animals dying with symptoms of collapse. If large doses are administered, fatty degeneration of the liver and kidneys occurs. Rabbits tolerate the same dose without any demonstrable injury whatever. Blood changes, especially formation of methaemoglobin, have never been observed. A dose of 0.1 gm. per kilo. injected subcutaneously causes death which is apparently due to anæmic symptoms.

Chemotherapeutic studies. The therapeutic efficacy of the drug was evaluated in bird malaria by Roehl. He worked out a method of using canaries for experiments on lines closely approaching the conditions of practical therapy so that it was possible to try out and assess in the laboratory many groups of drugs. Here it was shown that in bird malaria, the therapeutic index of atebrin was 1:30. Plasmoquin has the same therapeutic index whereas quinine has an index of only 1:4. Atebrin therefore is four times as effective as quinine. Chopra and Das Gupta (1933) carried out elaborate studies on the action of atebrin on plasmodium infections in monkeys and have come to the following conclusions.

Destructive action on the plasmodium. The destructive action of atebrin on this plasmodium appears to be exceptionally powerful. Usually two doses of 0.025 gm. each given either intramuscularly or intravenously are sufficient to control a very heavy infec-

tion which may amount to a million parasites per c.mm. The drug equally effects both the schizogony and the gametogony of this plasmodium and all phases of the parasite disappear rapidly from the peripheral circulation under its action. Even after a single dose, signs of degeneration are seen in the parasites and their numbers rapidly decrease. After two or three doses they disappear from the peripheral blood altogether.

Owing to its slow excretion atebirin, when given intravenously, appears to exert a more prolonged action than quinine on *P. knowlesi*. Our observations show that intravenous injections of quinine are not effective against a heavy infection with this plasmodium in *M. rhesus* unless they are repeated at short intervals, say of three or four hours, but one injection of atebirin suffices. It would appear that the growth of the parasites is not checked by quinine, probably because of its rapid excretion after intravenous injection.

Relapses. Atebrin has earned a great reputation as a powerful remedy in preventing relapses in all species of human malaria. Green (1932) treated 15 cases with 0.1 gm. of atebirin thrice daily for five days with no relapses, while there were 13 relapses among 24 controls treated with quinine. James and his colleagues (1932) treated 15 experimentally infected cases with similar doses and only one relapsed, four of them were chronic cases and had had several relapses prior to treatment with atebirin. Five cases infected at Horton with the 'Rome' strain of *P. falciparum* had no relapse after a course of atebirin, but two controls treated with quinine relapsed. Similar results have been recorded by Sioli, Hooper, De Uells, Jains and many others. In view of this evidence, the drug would appear to be more effective than quinine in curing malaria and preventing relapses, but so far as relapses are concerned this is not our experience with the Indian strains of malaria.

Whatever may be the case with human malaria, in monkey malaria relapses undoubtedly occur. In *M. rhesus* infected with *P. knowlesi* even after 5 days intensive treatment with large doses of the drug, the parasites invariably reappeared in 10 to 15 days and multiplied with the same rapidity as in the primary attack, causing death of the animal if prompt treatment is not given. The recrudescence can however be checked much more easily than the original attack. One dose as a rule suffices to control the multiplication of the parasites though a low grade of infection persists for a long period. After such a dose the parasites appear to lose their virulence and either a scanty infection may persist or the parasites may disappear from the peripheral circulation for long periods without further treatment. Whether in course of time they will regain their virulence is now being studied.

Effectiveness against malaria. The, antimalarial efficiency of the drug was first tested by Prof. Sioli in paralytics artificially infected with benign tertian malaria. He administered the preparation to patients on 3 consecutive days and found that 0.1 gm. three times a day can effectively control the symptoms and cause a disappearance of the parasites. The drug has now been tried in various countries, including the tropics, subtropics and temperate zones.

The toxicity of atebtrin is low, with a wide margin of safety between the effective therapeutic dose and the toxic dose. The new product has been investigated very thoroughly. Unlike plasmoquin, it acts on the asexual forms of the parasites, in which respect it resembles quinine, whereas its therapeutic activity is said by some authorities to be even greater than that of that alkaloid. As atebtrin is more effective than plasmoquin in destroying the ring forms, the formation of crescents may be combated by a combination of the two drugs—0.1 gm. of atebtrin and 0.01 gm. of plasmoquin. Such a combination has been tried but in some cases toxic and even fatal results have been observed. The chief symptoms observed in mild cases are cyanosis and palpitations, but in some cases they resemble severe plasmoquin poisoning. It appears that combination of these two drugs increases their toxicity.

Clinical experiences with atebtrin in the Federated Malay States are also very encouraging. Green, working at the Institute of Medical Research, Kuala Lumpur, tried atebtrin in 50 cases of malaria. He found that in atebtrin-treated cases, the asexual parasites disappeared from the blood within seven days but quartan gametocytes tended to persist after the seventh day. In subtertian cases the gametocytes seemed unaffected by the drug. The conclusion drawn by this worker is that this new drug is definitely more effective than quinine in preventing relapses, when used for short courses of treatment.

Chopra and his co-workers (1933) carefully tested this drug on the Indian strains of malaria and have come to the following conclusions:—

(1) Atebrin is an effective drug in the treatment of Indian strains of malaria. Its destructive action on the asexual forms

of benign tertian, malignant tertian, and quartan types of malaria is about equal, the schizonts disappearing from the peripheral circulation after 0.6 to 0.9 gm. of the drug, *i.e.*, the administration of 3 tablets of 0.1 gm. for 2 or 3 days.

(2) The sexual forms or gametocytes are more slowly acted upon than the asexual forms. The gametocytes of the benign tertian and quartan types are readily destroyed and degenerative changes can be observed in them shortly after the administration of the drug is started. The gametocytes of the malignant tertian type, *i.e.*, crescents, are not affected at all.

(3) The drug is effective in doses of 0.1 gm. three times a day, the course lasting for five days, making a total of 1.5 gm. of the drug for the cure. In the majority of patients such a course is effective, but in a few of the persistent ones it may have to be repeated after a few days interval. The drug can also be effectively given intravenously in doses of 0.1 gm. dissolved in 1 to 2 cubic centimetres of distilled water when the number of parasites in the peripheral blood is large.

(4) In chronic types of malaria the drug is effective and produces a rapid reduction in the size of the spleen.

(5) Atebrin is reported to prevent relapses, but the evidence at our disposal shows that this is not the case with Indian strains of malaria. Its prophylactic value is very similar to that of the cinchona alkaloids.

(6) The blood pressure is lowered in some patients during the administration of the drug, but in the majority it has no effect. The pulse rate and respiration are not markedly affected. It has been used in patients suffering from endocarditis and myocarditis without ill-effects.

(7) The action of atebrin closely resembles that of the cinchona alkaloids and the introduction of this drug is a distinct advance in the treatment of malarial fevers in India. The price at present is too high for its use by the people in general.

Relapses. It has been urged that the most valuable property of atebrin is its power to prevent relapses and many workers have borne testimony to this effect. But in the author's experience quite a number of patients, at least five out of a series of 39, apparently relapsed. It must be pointed out how-

ever that in a malaria endemic area such as Calcutta, it is very difficult to be certain whether these were fresh infections or relapses. Two patients relapsed while they were actually under observation in the hospital after the course, and parasites of the same species were found in the peripheral blood. (A number of relapses were also reported in the patients treated outside the hospital). Even though these may not be real relapses but fresh infections, it may be noted that infection took place before the atebtrin had been fully excreted from the body of the individual. Although in an endemic area like this, it is difficult to prove in the human patients that relapses actually did occur after a course of atebtrin, there is ample evidence in experimental malaria in monkeys (*M. rhesus*) that the drug does not eradicate infection from the body and that relapses are common. In quite a number of these animals after a course of the drug and disappearance of symptoms and parasites from the peripheral circulation, the parasites reappeared usually within two weeks and the animal showed symptoms of the disease.

Prophylactic uses. Atebtrin is claimed to have prophylactic properties and has been used by some workers for this purpose with good results. It is said to have been continued for months in doses of 0.1 gm. daily without producing any untoward effects. It has also been combined with plasmoquin for this purpose, 0.1 gm. of atebtrin and plasmoquin 0.01 gm. being given together daily. The prophylactic value of atebtrin is still under investigation, but so far as we can see it has no more true prophylactic action than the cinchona alkaloids.

The results of experimental trials with atebtrin are precisely the same as those with plasmoquin. Atebtrin in the usual curative doses (0.3 gm. daily for 5 to 8 days) controls the infection to the extent of making it latent for a long period. As these doses of atebtrin are much smaller than those liable to cause toxic symptoms, it is to be preferred to plasmoquin, where the prophylactic dose is the maximum that can be tolerated. A daily dose of 0.1 gm. of atebtrin has proved more effective in keeping infected persons free from fever, than a daily dose of 0.3 gm. (5 gr.) of quinine. The continued use

over a long period does not produce any untoward effects except that there may be a yellow coloration of the skin.

Blackwater fever. Atebrin can be given to patients suffering from blackwater fever without ill-effects. It can also be given to patients who are sensitive to quinine and in whom administration of quinine produces hæmoglobinuria.

Untoward and toxic effects. Atebrin unlike plasmoquin is not a very toxic drug. Double the usual dose of 0.3 gm. per day (*i.e.*, 0.6 gm. in 24 hours) can be tolerated, but larger doses may produce gastro-intestinal irritation. In spite of the tendency referred to above of accumulation of the drug in the system, the author gave two five day courses of the drug with a few days interval between without producing any toxic effects, and with therapeutic benefit. Some patients complained of slight pain or a sensation of uneasiness in the epigastric region soon after taking the drug. This generally started on the second or third day and persisted as long as the drug was being administered. The pain was never so severe as that produced by plasmoquin. In none of our series did we get the severe abdominal pains described by Green (1932). A number of our patients complained of headache and loss of appetite while the drug was being given, but this also passed off when atebrin was stopped. In some patients a profound feeling of general depression started on the third day of treatment and persisted for several days after the drug was stopped. The patient felt as if he had 'no life in him' and had no desire to make physical exertion and wished to remain lying down. In some of the patients diarrhoea was produced on the second and third days of treatment and persisted while the drug was being given. The diarrhoea was of a mild type and no particular treatment was necessary. It stopped with the cessation of the drug. In a few patients, especially those who were obese, palpitation occurred which was quite distressing, but it stopped when the drug was discontinued and in one patient cardiazol had to be administered. In one case mental disturbances are reported to have occurred. A yellow staining of the skin and conjunctiva occurred in several of our patients, but the colouration as a rule was very slight and in none of the patients did it amount

to a jaundice-like appearance. It is not true jaundice. There is no slowing of the pulse or bile pigment in the urine. It represents excretion of the drug by the skin and is merely a yellow discolouration of which the patient is often unaware.

Relative value of atebryn and quinine. Quinine, probably the most useful of the cinchona alkaloids, does not produce the same effect on all species of malarial parasites; it is most potent on the parasites of benign tertian malaria, less active on those of quartan and least of all on those of subtertian malaria. It produces rapid alleviation of the clinical symptoms, but in a number of cases it does not destroy all the parasites, even after a prolonged course it is not toxic in the doses in which it is usually given, but it is not pleasant to take and in many individuals it gives rise to unpleasant symptoms.

Atebrin on the other hand is not unpleasant to take and does not usually give rise to toxic symptoms; where comparatively large doses are used and excretion of the drug is delayed, a yellowish discoloration of the skin appears, but this is of the nature of carotene pigmentation and disappears within 8 to 15 days. Atebrin compares favourably with quinine in ridding the blood of malarial parasites and in relieving symptoms. Atebrin, like quinine, destroys the gametocytes of *P. vivax*, but neither of these two drugs has any action on the gametocytes of *P. falciparum*. Its use, however, over a period of seven days or less destroys the gametocytes of *P. vivax* with sufficient rapidity to prevent mosquitoes becoming infected from benign tertian cases within three or four days of commencing treatment. Among gametocyte carriers of *P. falciparum* neither atebryn nor quinine may be regarded as an efficient drug in preventing the infection of mosquitoes which have access to such patients under treatment.

TEBETREN AND MALARCAN

Hydroquinine or methylhydrocupreine, $C_{20}H_{24}N_2O_2$, is obtained by the hydrogenation of quinine, $C_{20}H_{24}N_2O_2$. A combination of this with an acridine dye and a bile salt has been introduced under the name of Tebetren, which is described as methyl-hydrocupreine-methyl-acridine-dehydrocholate.

The bile salt is said to render the compound less toxic. Malarcan is a preparation of similar nature prepared by an Austrian firm. The drug is available for oral administration in tablet forms of 3 grains each and in ampoules of 2.1 c.cm. and 1.1 c.cm. for parenteral administration.

Stoute (1930) reports a trial of tebetren in about 100 cases, adults and children. The course for adults was two tablets (6 grains), and for children quarter to one tablet according to age, every four hours for thirty doses; four courses were given with a rest of three to five days between courses. Certain by-effects were noticed, such as a feeling of fullness in the head, deafness, and ringing in the ears but these were restricted to the first course. In benign tertian and subtertian the parasites disappeared in about half the time that they do with quinine. Cases resistant to quinine reacted well to tebetren. Cured patients, when safeguarded from re-infection, did not relapse during eighteen month's observation. Subcutaneous injections caused sloughing but intramuscular injections produced no reaction. Barrowman (1933) in the Malaya States found that tebetren is paracitidal to both sexual and asexual forms of all types of malaria. While this may be true of benign tertian and quartan types, the sexual forms of malignant tertian type of Indian strains of malaria are not destroyed by this drug.

Chopra and his co-workers tested malarcan in a series of cases. The drug controlled the clinical symptoms of malaria in much the same way as quinine but parasites took longer to disappear and relapses were more common. It has no effect on the sexual forms of malignant tertian parasites.

Quinoline compounds. Research is still proceeding with a view to the discovery of new antimalarials among the quinoline derivatives. Slater (1930) reports further on quinoline compounds containing arsenic and has prepared several derivatives of quinoline-arsenic acids, which are being tested by the Joint Committee on Chemotherapy formed by the Medical Research Council and the Department of Scientific and Industrial Research in respect of their action on malarial parasites. A number of these compounds has been prepared in India and they are being tested by the author.

OTHER DRUGS USED IN MALARIA

Certain drugs are believed to have some influence in causing the parasites to disappear from the peripheral blood or perhaps in assisting the patient to resist the invasion of the parasites. These drugs can be divided into two groups: (1) those which are given in combination with quinine and (2) those which are given by themselves especially where quinine is not tolerated.

1. Drugs used against malaria in combination with quinine.

(i) Preparations of Arsenic, Antimony, Iron, and Mercury.

Various preparations of arsenic are frequently used in the treatment of malaria. Of the various *inorganic preparations*, liquor arsenicalis (Fowler's solution) and a combination of arsenic, quinine and iron, either in the form of a pill or a mixture have been prescribed. *Mistura arsenii quiniæ et ferri* (Baccelli's mixture) is one of these preparations and it is given in doses of $\frac{1}{4}$ to 1 oz. (15 to 30 c.cm.). Arsenic in inorganic form has been shown to have no action whatever on the malarial parasites.

Organic preparations of arsenic are said to have a marked effect on some of the pathogenic protozoa and are believed by some to have a destructive effect on the malarial parasites. *Neo-arsphenamine* is said to abort the symptoms in practically every attack of malarial fever and thus save the patients from getting attacks of fever which are very debilitating. The convalescence is shortened and the chances of recovery are enhanced. They also have an excellent tonic value and the patients recover quickly and return to work. *Sulph-arsphenamine* in doses of 0.3 to 0.5 gm. subcutaneously or intramuscularly is also effective. Some clinicians combine intravenous injections of arsenicals with quinine as a routine treatment of malaria.

Sodium cacodylas even in doses of 10 grains intravenously had no effect either on the parasites or on the temperature independently of quinine. *Arrhenal* or *new cacodyls* in doses of 8 grains by the mouth proved ineffective. *Soamin* and *arseno-benzol compounds*, *stovarsol* and *treparsol* have been frequently tried either alone or in combination with quinine. The hope that they would be a substitute for quinine has not been fulfilled although some consider that they are effective against benign tertian (*P. vivax*) affections in the acute stage. One gm. of the sodium salt of *stovarsol* in 10 c.cm. of distilled water given intravenously cleared the blood of *P. vivax* in seven artificially infected and two naturally infected cases and prevented relapses for two months. The drug acted better on old pigmented parasites, the older schizonts and the gametocytes. Sinton (1927) treated 25 cases of benign tertian infection with *stovarsol* giving up to 4.0 gm. in 5 days; 92 per cent. relapsed. According to Marchoux, the brothers Sergeant, Cluca and Alexa and others, *stovarsol* is without effect on the parasites of quartan and malignant tertian fever. Some

observers report that its use as an antimalarial remedy has been followed by secondary effects (intestinal disturbances, cutaneous reactions and nephritis), others that it has an excellent action in improving the general health of malarious patients.

Quiniostovarsol. When it was found that arsenical preparations in general have only a feeble action on malaria parasites, it became the custom to combine these remedies with quinine. The mixtures chiefly used are *quiniostovarsol* (Fourneau) and *quinine troposan* (May and Baker). On behalf of the Malaria Commission several workers have made clinical trials with quiniostovarsol. Unfortunately the results reported by different observers are not comparable, because there were great differences in the doses and periods of administration of the drug. The general trend of opinion seems to point to the fact that these drugs are not of much use.

The view held by some observers that *tartar emetic* or other compounds of antimony have an effect on the malarial parasites has now been abandoned, though some of them still hold that they may be useful in preventing relapses.

Mercury compounds such as *perchloride*, *mercurophen*, *mercurosol* and *mercurochrome 220* have been tried in the treatment of malaria without success. They have no curative action in human or avian malaria. In the old days ague was treated with large doses of calomel. It has also been observed that syphilitics, who are saturated with mercury, do not get attacks of malarial fever and for this reason biniodide of mercury by the mouth, in pill form combined with injections of perchloride of mercury has been recommended. The results however are not convincing.

Mercurochrome. Intramuscular and intravenous injections of mercurochrome have been tried in the treatment of malaria. A 0.5 to 1.0 per cent. solution is generally employed, the dose being 0.003 gm. per kilo. body weight. The blood is said to become negative to parasites but this is doubtful. Occasionally it produces flushing, headache and hyperpyrexia.

Coal tar preparations. *Methylene blue*. The use of medicinal methylene blue (methylthioninæ hydrochloridum) against malaria was first suggested by Ehrlich and Gullaman. It has been tried by many observers with varying results. The preparation used should be free from metallic impurities, especially zinc chloride which may cause vesical and rectal irritation. The drug is given in doses of 1 to 4 grains (0.06 to 0.26 gm.) in cachets or capsules 3 or 4 times a day for a week or more, the total daily dose not exceeding one gram. It is excreted in the urine which becomes blue and the stools also turn blue on exposure to air. Many workers have tried it in all forms of malaria without success, while others believe it is a substitute for quinine especially in mild cases of malaria. It is said to be especially useful in

cases refractory to quinine. In the pernicious type methylene blue has been given combined with quinine intravenously, 5 c.cm. of 1 per cent. solution being injected. A dose of 0.2 gm. given in this way followed by neo-arsphenamine four hours later, reduced the relapse rate. Couto (1926) believed that methylene blue is as efficient as quinine in the treatment of benign tertian, but that it had no effect on the malignant tertian parasites. Given subcutaneously it causes abscess formation. Other authorities consider that although it is useless by itself in the treatment of malaria, when combined with quinine it helps to prevent relapses and the therapeutic dose of quinine can be greatly reduced. Recently, it has been tried in doses of 0.2 gm. three times a day at two hour intervals, in the treatment of quartan malaria which does not yield to quinine so readily as the other forms. The author has tried a combination of quinine with methylene blue in quartan infection and considers it superior to many other forms of treatment.

Carbolic acid preparations. Liquid carbolic acid 6 to 12 minims daily for a period varying from 4 to 6 weeks have been tried in the treatment of benign tertian malaria but the results are not promising.

Preparations of hypochlorous acid. *Eusol* or liquor hypochlorous co., which contains approximately 0.027 per cent. of hypochlorous acid was tried in cases of malaria which appeared to be refractory to quinine. Forty c.cm. of a freshly prepared solution were given intravenously, but the drug did not appear to produce any effect either on the parasites or on the fever. Quinine has also been combined with iodine, especially in the treatment of chronic malaria.

Quinine does not act efficiently when the liver is not active. For this purpose it has been combined with such drugs as calomel, rhubarb, aloes. Warburg's tincture contains aloes, rhubarb, saffron, gentian, ginger, cinnamon, camphor, pepper and a number of other things along with quinine sulphate. In doses of half an ounce 2 or 3 times a day on an empty stomach it is quite effective in the treatment of malaria.

Organotherapy. Organotherapy has been used as an aid to quinine treatment. Preparations made from bone-marrow and suprarenal gland have been tried. Bone-marrow extract may be given in the form of tablets, 1 to 3 being given daily, or as a glycerin extract which is sold under the name of 'marrabain.' It has been suggested that low blood pressure in pernicious malaria is due to inefficiency of the adrenal glands and for this reason suprarenal gland extract has been given internally. Injections of adrenalin have also been used for constricting the blood vessels in certain organs and dilating them in others so as to flush them with blood containing quinine. Intravenous injection of adrenalin beginning with 0.01 mgm. and gradually increased to 0.3 mgm. or rarely 0.2 mgm. have been given in the treatment of splenomegaly. As many as 40 injections may be required to reduce the size of the spleen. Dessicated spleen substance has also

been used in doses of 3 to 10 grains daily. Pluriglandular extract, *i.e.*, a combination of suprarenal, spleen, pancreas and thyroid has been used on theoretical grounds.

Radio-therapy. Radio-therapy has been advocated especially in the splenomegaly of malaria, applications being made over the region of the spleen. In chronic cases the effect on the spleen is appreciable. In acute cases heavy dosage is dangerous. Taking into consideration the length of treatment, its difficulties and inconvenience, it should be rejected in favour of quinine and arsenic only.

2. Drugs used against malaria independently of quinine.

A number of medicinal plants have been used in the treatment of ague in India for centuries, but none of them have shown any special effect on the malarial parasites. A brief description of some of these remedies which have been tested by modern scientific methods is given below:—

Vitex peduncularis. This plant grows largely in Bihar, Eastern Bengal and the Central Provinces but it is not very well known. The aboriginal tribes of these localities believe it to have curative properties against malaria, blackwater fever and kala-azar. In Hindi it is known by various names,—*Nagball*, *Nagphani*, *Charaigora*, *Chhagrlaruba*, *Mit-jurgorwa*, in Bengali it is called *Baruna* and *Goda*.

The only reference by the old writers regarding its medicinal properties is its use for external application for pains in the chest. Vaughan (1921) found that the aboriginal tribes of certain parts of Bihar were well acquainted with this plant, and used it in the treatment of malarial fever and also of blackwater fever. They prepare an infusion of the leaves, of the root-bark or young stems and take it internally several times a day with much benefit. Preference is given to the dark-coloured-root plant over the pale-coloured variety.

Vaughan (1921) tried this drug in a series of cases in both these diseases and reported that it gave very satisfactory results. Chopra, Knowles and others (1924) carefully tested the drug and found it has no effect whatever in malaria.

Peganum harmala. Two alkaloids named *harmaline* and *harmine* occur in *Harmal* or *Peganum harmala*, which grows in abundance in Northern India, possess pharmacological action very similar to quinine. In acute malaria the action is not so pronounced as that of quinine, but harmine is said to have been successful in cases of relapsing malaria where quinine had failed. The writer has tried harmaline in doses of 5 to 10 grains daily without any effect.

Alstonia scholaris. Alkaloids named *ditamine* and *echitamine* are obtained from *Alstonia scholaris*. This plant grows all over India and is said to have strong anti-malarial properties. It has however been found ineffective. *A. congolensis*, *A. macrophylla*, and *A. constricta* are rich in alkaloids and have all been tried.

Berberis aristata. *Berberis aristata* (Rasaut) which grows on the Nilgiris and in the Himalayas contain two alkaloids named *oxycanthine* and *berberine*. Both *Alstonia* and *Berberis* were largely used in India and the eastern colonies in the treatment of malarial fever and are said to have beneficial effects. Waldrop (1927) advocated berberine as a provocative in latent malaria and considered it a specific in splenomegaly. The author tried berberine sulphate in doses of 3 to 4 grains 2 to 3 times a day in the treatment of malaria without success.

Other drugs that have been used in the treatment of ague in the indigenous system in India are *Cæsalpinia bonducella*, *Calotroptis gigantea*, *Hydrocotyl asiatica*, *Melia azadirachta*, *Soymida febrifuga*, *Andrographis paniculata*, *Aconitum napellus* and *Picrorrhiza kurooa* but none of them appear to have any marked antimalarial properties.

Holarrhena antidysenterica. The bark is used in some part of India in the treatment of malaria. The author has tried the alkaloid isolated from the bark, without effect.

Opium and narcotine. Opium is said to assist the action of quinine but there appears to be no foundation for this belief, though it undoubtedly ameliorates the many disagreeable symptoms of this disease. Dr. Roberts (1895) pointed out that the alkaloid *narcotine* or *anarcotine*, which occurs in large quantities in Indian opium possibly has antimalarial properties. As early as 1857 Dr. Palmer treated over 500 cases with narcotine in doses of 1 to 3 grams daily with apparently satisfactory results and for many years this alkaloid was used in the treatment of malaria. Chopra and Mukherji (1930) tried the drug in a series of cases of all forms of malaria, in the Carmichael Hospital for Tropical Diseases, doses ranging from 6 to 12 grains daily and came to the conclusion that this alkaloid has no antimalarial properties whatsoever. Opium addicts taking such large doses of opium as 20 to 30 grains daily get attacks of malarial fever.

A number of proprietary remedies have been recommended for the treatment of malaria.

Smalarina. Six to 8 tablets daily for a month have been tried but are not effective. The drug is liable to produce nausea, vomiting and diarrhoea.

Peracrina 303. According to some, the pills consist of a mass of yeast and a little starch stained with a yellow dye. According to others it is a combination of albumin with 10 per cent. trypanflavin. A course of treatment lasts for 3 months, the maximum dose being 12 pills per day. The drug is expensive and is not effective against an attack nor does it prevent relapses. This substance has been largely used in the treatment of malaria in Russia. It is liable to produce colic, diarrhoea and loss of appetite.

Plaudismol is a yellow liquid with a disagreeable smell and a taste both acid and sweet. It comes from the Argentine and contains extracts of *Senecio saliginus*, *Laeselia coccinea* and *Colliandra grandiflora*. It has no therapeutic value in malaria.

Chininphylin. It is quinine salt of mosithexamin phosphoric acid containing 58 per cent. of quinine base; it is said to be as valuable against malaria as quinine.

Elevasan Albert 102 is another one of these remedies.

Urotropine. Malarial coma has been treated with 3.0 c.cm. of a 40 per cent. solution of urotropine intravenously. It is suggested that formaldehyde derivatives hinder adherence of damaged erythrocytes to the wall of the blood vessels and this restores circulation in the blocked vessels.

Fourneau 664 is a compound allied to plasmoquin. It is given intramuscularly and is effective against benign tertian malaria. Doses of 0.04 gm. daily are ineffective and 0.1 gm. is dangerous. The drug is not satisfactory.

Fourneau 712 is a yellow powder soluble in water. It is very active against *P. vivax*, 0.04 gm. daily clearing up the parasites from the peripheral blood. It has no action on the malignant tertian parasites.

R 110 and R. 123 are quinoline preparations. These drugs can be given by the mouth subcutaneously or intramuscularly. They are still in the experimental stage.

CHAPTER XXVI

PRESENT POSITION OF ANTIMALARIAL DRUG THERAPY

The present views regarding the treatment of malaria can be stated by giving the following extract from the Third General Report of the Malaria Commission of the League of Nations (1933).

Treatment of the attack. It has already been indicated that, in an endeavour to treat an attack of malaria successfully, or to assess the relative efficacy of different systems of treatment, various conditions which influence the therapeutic action of antimalarial remedies must be taken into consideration. Among the most important are:—

(1) The species of parasite concerned; (2) the particular geographical race or strain of the parasite; (3) the dose of infection; (4) the stage of the disease—whether it is a primary attack or a relapse; (5) the degree of natural or acquired resistance to malaria possessed by the patient.

Without entering into detail, it may not be out of place to indicate what recent additions to knowledge on these subjects are of importance from the point of view of treatment.

(1) The desirability of investigating separately the therapeutic effect of antimalarial remedies on each of the different species of the parasite is everywhere recognised, and modern practice endeavours, as far as possible, to supply the results in practice. From the point of view of economy in the consumption of quinine, the importance of prescribing a plan applicable to all has become greater since the discovery of *P. ovale*. As a general rule, this parasite is so 'benign' that only one or two small doses of quinine suffice to cure the attack.

(2) About the variations in clinical virulence of different geographical races of the same species of parasite, it may be recalled that, as long ago as 1900, Grassi recognised two distinct clinical varieties of Italian malignant tertian fever, and named one of them *mitis*, which means mild, to other *immitis*, which means severe. Since then, many observers have noted remarkable differences between the malignity of malaria caused by *P. falciparum* in different parts of the world. From one part of British India it has been reported that *P. falciparum* in its schizogony cycle is the most amenable of the three species to quinine therapy, while from another part quite the contrary opinion has been recorded.

In recent years, a study of this subject in cases of human malaria intentionally infected with known strains of *P. falciparum* from different countries has yielded interesting results. It has been found for example, that, to control the primary attack of malignant tertian malaria infected with a Rome strain of *P. falciparum*, it required eight times as much quinine as was required to control cases infected under precisely the same conditions with an Indian strain. Again, it has been found in the Netherlands that various geographical races of *P. vivax* react differently to the same remedy. These and other results afford a reasonable explanation of contradictory observations on the therapeutic efficacy of the same plan of treatment conducted in different countries, and indicate the importance of local therapeutic investigation. Field workers and hospital physicians in all malarious parts of the world should endeavour as soon as possible to add to existing information the clinical virulence and amenability to quinine of the particular strains of *P. falciparum*, and of other species prevalent in the countries where they work.

(3) What influence the dose of infection may have in relation to the therapeutics of malaria is a problem about which little information is as yet available. In general, it is believed that primary attacks of malaria caused by the bites of many mosquitoes are more difficult to control by quinine than are primary attacks caused by the bite of only one or two insects. In this connection, an important result of experimental work is that it has been found possible, by causing many mosquitoes infected with *P. ovale* to bite the same person repeatedly over a period of several days, to produce even with this very benign parasite a severe clinical and parasitological attack, for which specific treatment must be promptly given.

(4) and (5). For selecting the best treatment in a case of malaria, nothing is more important than a knowledge of the stage of the disease. Quinine has no appreciable effect when given during the incubation period, and it has little effect when given on the first or even on the second day of the 'initial fever'. It is much more effective after the patient has had several paroxysms of fever than at an earlier stage, and its effect is greatest when the fever and parasites are beginning to decline as a result of the natural defensive mechanism which normal human beings possess. A relapse is always more amenable to quinine than a primary attack. The reason why a cure is more easily brought about by quinine in the later than in the earlier stages is that persons who pass safely through a few paroxysms quickly acquire a defensive property, which counteracts to a great extent the harmful effects of the parasite. The practice of malaria-therapy has thrown a good deal of light on this subject by showing that persons who have passed through ten or more severe paroxysms of benign tertian malaria without receiving any quinine have already acquired such a high degree of natural

defensive power that a few small doses of quinine suffice for the temporary cure of the attack. Treatment should aim at assisting malaria patients to acquire as much as possible of this defensive power (sometimes called 'tolerance,' 'immunity' or 'premunition'). With this object, an endeavour should be made to ascertain precisely the stage of the patient's disease, and to prescribe the doses of quinine which are just sufficient to be effective in that particular stage, without at the same time interfering with the patient's defensive mechanism. To give large doses of quinine indiscriminately to all cases of malaria is a grave error. The selection of the correct dosage for particular stages of malarial attacks, with due attention also to the species of parasite concerned and the virulence of the local strain, is an important item in the modern method of treating malaria. It will be mentioned again when describing general rules for treatment by quinine. All we wish to do here is to correct the common view that the earlier one begins specific treatment, the more successful will be the results. Except in very severe cases, in which the patient is almost overwhelmed by the parasitic invasion, and is therefore unable to acquire any defensive power against it, the truth is just the reverse. The same remark applies to relapses. It is a common belief that relapses are difficult to cure because they are late manifestations occurring in persons who have not been treated early in their primary attack, or who have been insufficiently treated with quinine in that attack. The truth is that relapses are always much more easily controlled than the primary attacks, because the patient already possesses some acquired defensive power. Indeed, as was pointed out long ago by Koch, Marchiafava and others, the risk of pernicious symptoms in malignant tertian fever is greatest in the primary attack and early recrudescences, because any person who has recovered from that stage of the disease has acquired sufficient defensive power ('tolerance' or 'premunition') to protect him, when he gets a relapse, against those disastrous occurrences.

General rules for treatment of the attack. Before dealing with the specific drug therapy of malaria, it is desirable to mention briefly some general rules to which attention must always be given if success in treating attacks of the disease is to be obtained. It is to be understood, however, that no attempts will be made to deal with this subject completely, or to indicate the treatment of complications such as heart-failure, delirium, very low blood-pressure.

The Commission wishes to emphasize the importance of insisting that persons who are liable to suffer from malarial attacks should go to bed as soon as they feel that an attack may be impending. In many cases there are premonitory signs, and it often happens that patients who go to bed with the onset of these signs, and take a purgative, followed by a therapeutic dose of quinine, can ward off the attack or escape lightly. The endeavour should be to get the patient

comfortably to bed, and in a condition which favours perspiration before the actual paroxysm of shivering begins. In most cases, it is sufficient for the patient to get under blankets with hot-water bottles, and to take first a full dose of a simple diaphoretic mixture, and then a cup of hot broth or tea.

Having made the patient as comfortable as possible, the condition of the stomach and bowels requires attention. Patients suffering from malaria are almost invariably constipated, and this condition must be corrected as early as possible if quinine is to produce its maximum effect. It will have to be decided whether it is practicable in the particular case to begin with clearing out the lower bowel by an effective enema; if this can be done, the patient will afterwards be much more comfortable, and less likely to suffer from nausea and vomiting. A drug should next be given which will act upon the liver, and will induce a free flow of bile, which is a good solvent of quinine. It must be followed within a few hours by a saline draught, and a dose of natural aperient water should be repeated each morning throughout the attack.

Next, attention should be given to the exact diagnosis of the type of malaria and the particular stage of the disease, with a view to deciding with what specific antimalarial remedy and in what doses, treatment will be begun. This subject (specific drug therapy) will be considered in a later paragraph.

Lastly, in addition to specific treatment, attention should be given to an endeavour to allay particular symptoms. Of the numerous drugs which have been tried for obviating cinchonism, it is said that caffeine given hypodermically or intravenously shortly before the administration of quinine, is the most effective. To relieve headache, phenacetin and similar drugs are often given, but they should be used with caution on account of their depressing effect on the heart. Headache is often greatly relieved when the bowels have been cleared by an enema. For nausea, a full dose of bicarbonate of soda taken in hot water and repeated at intervals is sometimes useful. *In all cases with severe vomiting, and in all cases in which there are signs of cerebral or other dangerous complications, a dose of the specific remedy should be given intravenously.* Quinine bishydrochloride 0.6 gm. dissolved in 5 c.cm. of physiological salt solution is a suitable dose for intravenous medication. Until it has taken effect the patient should be given ice to suck.

General management. During the hot stage, the temperature and general condition of the patient must be carefully watched; but knowing that in all probability the high temperature will not last long, it is less necessary to take very active measures to reduce it than in the continued fevers. Temperatures of 104.5° or 105° F. (40.3° or 40.6° C.) are common in benign tertian malaria, and need occasion no alarm, but a tendency to rise higher than this should be counteracted by tepid or cold sponging. If possible, however, we should do nothing which may delay the onset of the sweating stage, in which the patient gets almost

immediate relief. Shortly after the onset of this stage, the patient's wet clothing should be changed, and he may be given a stimulating drink. Usually, he will go to sleep for an hour or two, and wake in a bath of perspiration and very weak, but feeling that, at any rate for the time, his illness is over. When the hot stage lasts a long time, and there is distressing headache or restlessness, a hypodermic injection of morphia is the best treatment. While there is fever, the patient should drink as much fluid as possible (preferably soda-water, barley-water, and other alkaline drinks), and in all cases the urine should be examined frequently for albumin, blood and haemoglobin. Albuminuria is often only temporary, but if casts are present in the centrifugalized deposit, it must be regarded as a serious complication requiring careful dietetic, nursing and medicinal treatment.

Lastly, among these general rules the Commission desires to make the following remarks about the administration of the specific remedies :—

(1) The manner in which quinine acts in bringing about a disappearance of fever and parasites is not known, and this seems to be true also for the new synthetic remedies. But there is a general consensus of opinion that, to obtain the optimum action of specific anti-malarial remedies, the co-operation of the host's defensive mechanism is necessary, and that this mechanism may be greatly impaired—or, indeed, may be suppressed entirely—by giving the specific drugs in too large doses or during too long a period. As regards quinine, it has been proved that large doses are not more effective than moderate doses. On these grounds the Commission considers that large doses of quinine (and presumably of the new synthetic remedies) should be avoided, and that courses of treatment with curative doses should not exceed seven days and that treatment for five days will often suffice.

The Commission also wishes to say that, although it recommends that quinine should be administered intravenously in acute cases with dangerous symptoms, it strongly disapproves the practice of treating ordinary cases of malaria by intravenous or intramuscular injections of quinine.

(2) It thinks, also, that, after the clinical cure of a primary attack (which means, as a general rule, after curative doses have been administered for five to seven days), it is best to cease giving the specific drug for a time, in order that the secondary effects of the drug on the human body may entirely pass off. A person whose primary attack has been cured by a course of five or seven days' treatment with therapeutic doses of a specific remedy will certainly remain free from a recrudescence for at least a week, and no advantage whatever is derived from continuing to give the specific drug during that fever-free and parasite-free period. Neither treatment with quinine nor with any of the new synthetic drugs, however intensive the treatment may be, is a *therapia magna sterilisans*, and the same effect in preventing recrudescence

cences and relapses is obtained when an interval of a week or ten days is allowed to elapse between the end of the curative course and the beginning of the prophylactic course, as is obtained when the specific drug is administered continuously during that period.

(3) The Commission is of opinion that it is seldom or never in the best interests of patients to endeavour to combine a plan of treatment designed for the prevention of relapses with a plan having for its object the rapid clinical cure of an acute attack. In particular, they wish to suggest that caution should be exercised in adopting the practice of combining plasmoquine with quinine or with atebirin in the treatment of acute primary attacks. Plasmoquine in non-toxic doses is not considered to have an effective action on the asexual (fever-producing) stages of the malaria parasite (particularly *P. falciparum*), and the Commission suggests that, until more is known of its toxicity to patients who are suffering from high fever, and who are liable to have cerebral or cardiac complications, its administration should be deferred until the primary attack has been overcome.

Specific drug therapy. In addition to quinine and other preparations of cinchona bark, two synthetic preparations—namely, plasmoquine and atebirin (formerly named erion)—must now be classed as specific antimalarial remedies, which are being extensively used in many parts of the world. They are not to be regarded as substitutes for quinine, but as additional weapons for use in particular circumstances and for special purposes. What has to be understood and to be applied in practice is that each of the three specific drugs—quinine, plasmoquine and atebirin—has its own particular action on the malaria parasite in one or other phase of its life-cycle in the human host, and that what the physician should aim at is to select the correct drug and the optimum dosage for the particular purpose which he has in view. The particular purpose to be dealt with in this section is treatment of the malarial attack.

In considering this subject, it is important, in the first place, not to bring confusion into the problem by assuming that the physician who sets out to cure an attack of malaria must at the same time occupy himself with the task of preventing relapses. The two purposes (cure of the primary attack and prevention of relapses) are so entirely different that, in the opinion of the Commission, it is incorrect to endeavour to accomplish them both at the same time. The first object to be accomplished is to cure the attack from which the patient is suffering; when that has been done, attention can be given to the problem of relapses. These remarks are made because, in the opinion of the Commission, it is not a good practice to treat attacks of malaria in the acute stage with a combination of two of the specific drugs mentioned, in the hope that one of them will be effective in curing the attack, the other in preventing relapses. Particularly with regard to the growing practice of treat-

ing acute attacks with a combination of quinine and plasmoquin, the Commission's attention has been drawn to observations indicating that the toxic effects of plasmoquin seem to be enhanced by a condition of fever and anaemia. It is known that at least in malignant tertian fever plasmoquin is not effective against the asexual (fever-producing) stages of the parasite and it is suggested that the administration of this supplementary remedy should be deferred until the acute stage of the disease has been overcome.

Taking up the position, then, that the best practice in treating an acute attack is to employ only one specific drug, it has to be decided for the particular case concerned which of the three is to be preferred, and in what doses the selected drug is to be used.

At the present time, this question can be answered categorically for only one type of malaria—namely, *malignant tertian* fever caused by *P. falciparum*. There is a general consensus of opinion that, for treating primary attacks of this type of malaria, atebirin is very much more effective than quinine or any other remedy hitherto known. The usual doses are three tablets (each containing 0.1 gm.) daily by the mouth for five or seven days. As the drug is relatively non-toxic, a dose of six tablets (0.6 gm.) can be given on the first day if desired. In cases with severe vomiting or other complication which prevents oral administration, the drug can be given intravenously or intramuscularly in solution. It dissolves readily in normal saline. A suitable dose for intravenous administration is 0.3 gm. dissolved in 5 c.cm. normal saline. But the practice recommended by Professor Nocht and Professor Muhlens for treating severe cases is to begin with one or more intravenous injections of quinine, followed on the next and subsequent days by oral administration of atebirin. The opinion that atebirin is superior to quinine for the cure of primary attacks of malignant tertian malaria rests upon a large number of reports relating to natural cases treated in hospitals in the field, and also upon carefully controlled therapeutic experiments made in circumstances in which all the conditions were known.

It is to be understood, of course, that, in expressing the opinion that atebirin is the best of available antimalarial remedies for treating primary attacks of malignant tertian malaria, the Commission does not imply that good results cannot be obtained with quinine. In some parts of the world, the common strain of *P. falciparum* is of such low virulence that even small doses of quinine suffice for its cure. For example, as regards the strain which is common in one part of India, Knowles and his co-workers have said: "*P. falciparum* in its schizogony cycle is admittedly the most amenable of the three species of malaria parasite to quinine therapy." Experimental studies of cases infected intentionally with a strain from the area to which those observers referred have shown that, on an average, of the amounts of quinine used

in twenty cases, only 3 gm. of quinine given by the mouth, and spread over a few days, were required to cure the primary attacks and to prevent, in 25 per cent. of the cases, any subsequent relapse. A strain which is equally non-virulent appears to exist in some localities in West Africa. On the other hand, there are parts of India and Africa, as well as of Italy and other countries, where quinine is relatively quite ineffective against the local strain. It is in these localities particularly that the use of atebirin is desirable.

The answer to the question, 'Which is the best drug to select for treating primary attacks of benign tertian fever?' cannot at present be stated so definitely. In many countries, the prevalent local strain of *P. vivax* causes a relatively 'benign' primary attack with a tendency towards recovery, whether it is treated with specific drugs or not. Many statistical records of the percentage of cases of benign tertian malaria which in particular countries recover without specific treatment are available in the literature; Osler's estimate of 20 per cent. is often quoted. That different strains of the parasite are more or less susceptible to the action of specific remedies must now be regarded as having been established, and the knowledge makes it very difficult to compare the records of different observers satisfactorily. Probably the most virulent strain which is being worked with experimentally in the practice of malaria-therapy in Europe at present is the Madagascar strain used in mental hospitals in England since 1925, and also now being used in the Netherlands, Italy, Germany and Malta. Persons infected with this strain have to be kept under constant medical attention during the course, and must almost invariably be treated with a specific remedy when it is considered that they have passed through a sufficient number of febrile paroxysms. In hospitals where there is insufficient watchfulness and attention to the blood condition, the fatality due to this strain of benign tertian malaria is not less than 10 to 14 per cent. The comparative value of quinine bihydrochloride, atebirin and plasmoquin for treatment of primary attacks of benign tertian malaria caused by this strain has been examined by the method called 'abortion of the attack'. As between the therapeutic effect of quinine bihydrochloride and of atebirin when given at the same stage of the primary attack, not much difference can be observed. A single dose of atebirin (0.6 gm.) given between the seventh and tenth day of the attack will cause all the parasites to disappear, and the fever to cease within less than thirty-six hours, but a single dose of 0.6 gm. quinine bihydrochloride will produce the same good result. A more precise comparison of their relative efficacy could be made by using very small doses; but, as it is seldom or never the practice of physicians to use small doses of quinine for therapeutic purposes, the results would have little practical value. It appears from trials of atebirin and of quinine for the purpose of 'clinical prophylaxis' that in reality, a dose of 0.1 gm. of atebirin has

more effect in benign tertian malaria than a dose of 0.3 gm. of quinine, but therapeutic practice differs from prophylactic practice in that in the former it is a custom to use larger doses than are believed on scientific grounds to be sufficient. And when one uses a drug in doses larger than are necessary to effect the purpose desired, small differences between the comparative effect of different antimalarial remedies are not apparent. It has been shown definitely, for example, by comparative therapeutic tests under experimental conditions, that, in benign tertian malaria, no better effect can be detected when a dose of 2 gm. quinine (30 grains) is administered than when the dose is only 1.2 gm. (20 grains). For the same reason if, in comparing the therapeutic efficacy of quinetum with the therapeutic efficacy of quinine, one were to use daily doses of 30 grains (2 gm.) one would arrive at the conclusion that the therapeutic effect of either of these mixtures of alkaloids is equal to that of quinine. But by using minimum instead of maximum doses, it would be found that that conclusion is wrong. Apparent equality of action in tests with large doses results from the fact that the dose of mixed alkaloids although it does not contain 30 grains (2 gm.) of quinine, contains this alkaloid in sufficient quantity to produce the same therapeutic effect as is observed to result from its administration in that dose.

On these considerations the Commission does not consider that, for the treatment of primary attacks of benign tertian malaria, preference should be given to atabrin rather than to quinine. In the doses usually recommended, both are invariably efficacious. Each has some disadvantages, but they are trivial in comparison with their merits as antimalarial remedies. If it is desired to compare the relative cost of the two drugs for treatment of primary attacks of benign tertian malaria, the comparison should be between the cost of treatment comprising 1 gm., or at most 1.2 gm. (20 grains), of quinine bihydrochloride or quinine hydrochloride in tablets daily for five days and 0.3 gm. atabrin in tablets daily for five days. Using quinine, it is seldom necessary in benign tertian malaria to prolong the period of treatment of the primary attack beyond five days. For this reason the comparison should be with atabrin treatment for the same period.

So far as is known at present, the answer to the question "which of the specific drugs is best for the treatment of primary attacks of quartan malaria?" is much the same as that regarding benign tertian malaria—namely, that, because either of the remedies, quinine and atabrin are almost always effective, the choice between them must be decided on other considerations than those of immediate therapeutic efficacy for the clinical cure of the primary attack. A few cases of quartan malaria are surprisingly resistant to quinine, and it may be found that a few are resistant to atabrin. When one drug fails, the other should be tried.

In consideration of what has just been said, the Commission desires to suggest that the principal fact which should be kept in mind and applied in the practice of treating primary attacks of malaria is that two specific remedies instead of only one are now available. Neither of them complies with the requirements of a *therapia magna sterilisans*, and it would not be wise in the Commission's opinion, to decide that, for general routine use, one of them should be preferred to the other. The great advantage of possessing two curative drugs is that, in cases which seem to be resistant to treatment with one, trial of the other can be made. This, of course, is what should be done in practice. Everyone with experience of malaria in the tropics has encountered exceptional cases even of benign tertian or of quartan fever in which parasites can be found in the blood longer than five days after beginning a curative course of quinine, which usually results in causing all parasites to disappear by the second or third day. Such cases are those in which trial of the other specific might give a better result. The reverse is equally true. In a recent unpublished paper, Green working in Malaya, reports that, as yet he is not able to come to a final decision on the comparative efficacy of quinine and atabrin for the treatment of primary attacks of malignant tertian malaria. In one series of cases suffering from attacks caused by this type of malaria, ring forms of the parasite persisted in quinine treated cases for, on an average 2.8 days, and in atabrin treated cases 3.5 days. In a later series, ring forms persisted, on an average, in quinine treated cases 3.1 days and in atabrin treated cases also 3.1 days but it was said that in this series, the degree of infection in the atabrin treated cases was on the whole, lighter than in the quinine treated cases.

The use of plasmoquine in primary attacks. Nothing has been said as yet about the use of plasmoquine instead of quinine or atabrin for the clinical cure of primary attacks. For several years after its introduction plasmoquine was tried extensively for that purpose in doses of from 0.06 to 0.1 gm. or more daily for five days, and in some trials for much longer. It was reported in general that, in those doses, the therapeutic effect of plasmoquine for curing primary attacks of benign tertian and quartan fever was about equal to that of quinine, but that for curing primary attacks of malignant tertian fever its effect was by no means so good. It was found, moreover, that toxic symptoms were the general rule when those doses were employed, and that it was frequently necessary to reduce them or to suspend the treatment for a time. In a thorough trial with doses not exceeding 0.06 to 0.08 gm. daily, which was conducted on natural and induced malaria in Roumania in 1931, it was found necessary to suspend the treatment in 60 per cent. of the cases chiefly on account of cyanosis, excessive fatigue, profuse perspiration and cardiac troubles accom-

panied by attacks of vertigo and fainting. In a trial in India, suspension of treatment was necessary in twenty-two of twenty-nine cases, and it was found that some patients are more susceptible to the toxic effects of the drug than others; very strict medical examination of all patients at least once a day was considered to be necessary. Similar, and occasionally more serious, findings were reported from other countries, and as a result, it became a general rule not to use the drug for therapeutic purposes in larger doses than 0.04 gm. per diem. A common practice at present is to use it in even smaller doses (0.02 gm.) in combination with quinine. In these small doses it has little or no curative action on the asexual (fever producing) stages of the malaria parasite, and for this reason its use in the acute stage of a primary attack is difficult to justify. It was thought at first that a small dose given daily in the acute stage might prevent the development of the sexual forms of the parasite, which appear as a rule about the seventh day of the primary attack; but it has been found that the onset of crescents in the peripheral blood is not prevented or retarded even by larger doses of plasmoquin than it is customary now to give.

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SECTION IV

REMEDIES USED AGAINST SPIRAL ORGANISMS

The spiral organisms commonly met with in man can be grouped under the following heads:—

(1) **Spirillum**. This organism has got a rigid structure and the coils are preformed with terminal flagellum at each end.

(2) **Spirochæta**. This has a flexible structure and the coils are not preformed. The presence of flagella at the ends is doubtful.

(3) **Treponema**. Here the coils are very small, smooth and uniform with finely pointed ends.

(4) **Leptospira**. The primary coils in this organism are closely set and minute. It looks like a brilliantly refractile swimming bit of rope. The secondary coils are loose and open and with a tendency to loop at both ends.

The name spirochæte is employed as a general term for certain spiral organisms which have flexible bodies. The structure, morphology and nomenclature of these organisms are not definitely known. Schaudinn (1904) considered them to belong to the protozoal group. The work of Minchin and Woodcock (1911) and of the brothers Sargent (1907) has refuted the original hypothesis of Schaudinn. Dobell has grouped the spirochætes among the bacteria. As the position with regard to their classification is far from clear, the spirochætes will be considered in a separate section altogether.

The pathogenic spiral organisms of man may be classified as follows:—

1. *The blood-inhabiting spirochætes, viz., those of the relapsing fevers, and Spirillum minus, the parasite of rat-bite fever.*

2. *The Leptospira group including the parasites of Weil's disease, and Japanese seven-day fever.*

3. *The Treponema group including the spirochætes of syphilis and yaws.*

4. *Vincent's spirochæte, which together with the fusiform bacillus is responsible for Vincent's infection.*

The Relapsing fever spirochætes. The spirochæte of relapsing fever was first described by Obermeier (1873) and was named *Spirochæta Obermeieri*. Since then a large number of different species of the relaps-

ing fever spirochaetes, e.g., *S. recurrentis*, *S. duttoni*, *S. carteri*, have been described by workers in different parts of the world. It is very doubtful, however, whether these so-called species represent anything more than local races of one and the same spirochaete. Many distinguished workers have shown that it is impossible to distinguish the various strains from their morphological characteristics. It is better, therefore, to conclude that there is but one species of relapsing fever spirochaete, *Spirochaeta recurrentis*. The organism, when observed alive under dark ground illumination, shows the axis of its spiral nearly always straight and its coils uniform. When an infection is abating as the result of the development of antibodies in the blood, various coiled and clumped organisms may be found. In stained films, the spirochaetes show a very irregular appearance with widely open coils, twists, and every possible variation in type.

Spirillum minus, the cause of rat-bite fever, is commonly met with in India. This organism is found in the blood of infected mice, rats or guinea-pigs during the first two weeks and then becomes distributed in the connective tissues of the lips, nose, and tongue. It has been found that about 3 per cent. of house rats are carriers of the disease.

The Leptospira group. These organisms are characterised by the fact that the body consists of a spirally wound thread, the spirals being so fine that unless careful inspection is made they are overlooked. Under the dark-ground, the leptospira look like brilliantly refractile swimming pieces of rope. The two diseases due to leptospira infection in man are:—(1) Weil's disease due to *L. icterohæmorrhagica*, (2) Japanese seven-day fever due to *L. hebdomadis*.

Treponema pallidum. The spirochaete of syphilis has essentially the same structure as the relapsing fever spirochaetes, from which it differs only in being smaller and in having a larger number of coils for a given length. These are essentially parasites of the tissues and of the lymphatic system and include the following species:—(a) *Treponema pallidum*, the spirochaete of syphilis, (b) *Treponema pertenue*, the spirochaete of yaws, and (c) *Treponema cuniculi*, a spirochaete of the rabbit.

The discovery of the spirochæticidal power of arsenic and its derivatives marks the dawn of a new era in chemotherapy. The researches of Ehrlich and many other renowned workers that followed him were directed primarily to fight the organism of syphilis, i.e., *Spirochaeta pallida*. The success attained in this direction has practically solved the problem of spirochæta infections in all its protean manifestations.

CHAPTER XXVII

ARSENIC AND ITS DERIVATIVES

Arsenic is very widely distributed in nature. Some of the less active preparations of arsenic such as the sulphides, realgar (As_2S_2) and orpiment (As_2S_3) have been known in therapeutics since the beginning of the Christian era, but arsenic compounds were only brought into special prominence very much later when Geber in the Middle Ages prepared the active oxide, commonly called white arsenic (As_2O_3). Although arsenic was first used in medicine in England in the early part of the 17th century, its authentic history does not begin till Sir Thomas Fowler introduced Fowler's solution in 1786. Its employment in the treatment of protozoal diseases was first suggested by the famous explorer, Dr. Livingston as he recommended its use in the disease caused by the tsetse fly in animals.

Arsenic has been largely employed in art and commerce and on account of its ready accessibility it has been used for suicidal and homicidal poisoning. It was also used for spraying vines and other plants to protect them from attacks of insects and pests; but this had to be given up owing to its appearance in the wines produced from the plants so treated.

PHARMACOLOGICAL ACTION

Arsenic is toxic to all animals which possess a central nervous system and to most of the higher plants, but not to all lower organisms. Its antiseptic action is feeble and it is not classified as a protoplasmic poison. In 1 in 30,000 parts of water arsenic hinders the development of and eventually kills the algæ and the seeds of higher plants; moulds grow abundantly in 1 per cent. solution of potassium arsenite; alcoholic fermentation proceeds in the presence of arsenic although somewhat retarded at first. Arsenious acid is only one-tenth as strong an antiseptic as perchloride of mercury. Compounds of arsenic have no effect on the activities of such ferments as pepsin. Some of the pathogenic protozoa, *e.g.*, trypanosomes, show a most extraordinary susceptibility to arsenic and are destroyed in 1 in 200,000 dilution in the blood, while

free-living protozoa may survive in 1 in 5,000 solution. Malarial parasites are markedly resistant to the action of arsenic.

Local action. Arsenicals do not coagulate proteins nor change them in any way and, therefore, they produce very little irritation of raw surfaces and mucous membranes, but the cells die slowly after prolonged contact with them. They are for this reason used for destruction of exposed dental nerves and epithelial growths of the skin. When applied to mucous membranes and denuded surfaces, they produce much pain and deep destruction of the tissues. Arsenical dermatitis occurs among workers who handle it.

The unbroken skin is not affected by arsenic unless it is repeatedly applied or allowed to remain in contact with it for some time, when it may produce pustules or vesicles. In man, arsenic has a beneficial effect on the nutrition of the skin; the subcutaneous fat is increased and the complexion is improved; it renders the coat of domestic animals such as the horse thicker and more glossy. In veterinary medicine it is commonly used for this purpose and solutions of arsenic are used as 'dip' to rid animals of ticks, etc. Large doses cause eruptions and keratosis, but this is not due to vaso-dilator effects nor is there evidence of any action on the nerves. Arsenic compounds undoubtedly, during their excretion, have a marked action on the intestinal epithelium and it is probable that they also exert a specific action on the epithelial cells of the skin. The arsenicals also produce a brown colouration of the skin of the face and other parts which is known as 'melanosis'. This is not due to the deposition of an arsenic compound, but of some organic product in the deeper layers of the corium.

Alimentary canal. Small doses such as one-sixtieth to one-fiftieth of a grain of the oxide are said to increase the appetite and aid digestion; larger doses irritate the whole of the gastro-intestinal tract producing swelling and congestion of the mucous membrane. The mucous membrane of the stomach is generally red and swollen and often contains hæmorrhagic patches. One-fourth to half a grain produces gastric pain, nausea, vomiting and diarrhœa; after two or three grains the alimentary symptoms are much more intensified. Capillary paralysis is produced causing much exudation into the connective tissue; the epithelium is at first raised and can be easily rubbed off; then it is cast off as shreds or false membrane. The epithelium may also show cloudy swelling and fatty infiltration, and in some cases these are the only lesions present. The exudation poured into the lumen of the gut causes distension, increased peristalsis and profuse rice water stools; collapse and death may follow. These symptoms occur whether arsenic is given by the mouth or subcutaneously, though slightly larger doses are required by the latter route. The action on the alimentary canal is not of a corrosive nature but is a specific effect and there is a definite latent period.

Circulation. Very small doses have no effect on the isolated frog's heart, large doses depress it; the amplitude is at first increased but soon it is diminished; the rate may be slowed or quickened or become arrhythmic, the heart stopping in diastole; the effect seems to be a direct one on the cardiac muscle. The mammalian heart is little affected but large doses intravenously produce a fall of blood pressure due to paralysis and dilatation of the capillaries. This action on the capillary endothelium is direct as adrenalin and nicotine continue to raise the blood pressure after arsenic. Arsenic is thus termed a capillary poison. The vessels of the splanchnic area seem to be more susceptible to the action of arsenic than those of the rest of the body. Their dilatation leads to congestion of the bowels, fall of blood pressure and collapse. It has been experimentally shown that the capillaries are injured and become more permeable after arsenic poisoning. Intravenous injections of large quantities of saline cause oedema in animals to whom toxic doses of arsenic compounds have been given, while no such effects are produced in normal animals.

In therapeutic doses in man, little direct effect is produced. If continued for a long time, failure of the heart's action occurs as manifested by oedema of the feet, diminution in the quantity of urine and feeble, low-tension pulse. Degenerative changes in the heart muscle resembling those occurring in phosphorus poisoning have been shown to occur. The pronounced and persistent fall of blood pressure is partly due to cardiac failure and vasomotor depression, but chiefly to paralysis of capillaries. The flow of lymph in the thoracic duct is said to be increased by arsenic.

Blood. It is on the blood-forming organs that arsenic is believed to produce its most beneficial effects. The action is still obscure though it is largely prescribed in anæmia. Arsenic probably produces increased vascularity and stimulates the bone-marrow to increased formation of erythrocytes and hæmoglobin when anæmia exists. In pernicious anæmia it is said to increase the number of young newly formed red cells. With ordinary therapeutic doses however, no changes either in the erythrocytes or the hæmoglobin content have been observed in normal individuals nor in those suffering from chlorosis. Intravenous injections of organic arsenicals have no influence on the total or differential leucocyte count unless toxic reactions occur. A slight increase may occur sometimes a few hours after injection but at the end of 24 hours the count is again normal. In larger doses there is extensive degeneration of the cells of the bone-marrow and anæmia is produced.

It has been shown that in shed blood, small quantities of arsenites protect the red cells from various hæmolytic agents, and this may partly explain its beneficial action in diseases like pernicious anæmia. Experiments show that the presence of sodium arsenite in a concentra-

tion of 1 in 20,000 stops the hæmolytic action of distilled water or other toxins on washed red blood corpuscles, *in vitro*. In therapeutic doses arsenicals have no effect on the coagulability of the blood.

Respiration. Small amounts have a distinct stimulating effect on the respiratory centre; large amounts depress it. In arsenic poisoning in man the respiration is not affected until very late, but ceases before the heart, probably on account of the exhaustion of the centre from low blood pressure. Small doses are said to depress the peripheral terminations of the vagi in the lungs; hence it is used in asthma.

Central nervous system. In the frog a descending paralysis is produced, the animal first losing its spontaneous movements and then its reflexes; the terminations of the motor nerves become affected later on. In the mammal, no certain indications of any such action are forthcoming as paralysis and coma can be explained by the gastro-intestinal effects and capillary changes. In chronic poisoning, peripheral neuritis and characteristic lesions in the nerve trunks occur in man and animals and in severe cases the spinal cord may be secondarily involved.

Metabolism. With small doses there is increased assimilation and decreased katabolism which give rise to improved digestion and increase in the body weight; metabolism of carbohydrates is slowed and fat is deposited. If large doses are given it causes increased breakdown of tissues as shown by augmented excretion of nitrogen, sulphates and phosphates in the urine. It is not clear whether this increase is due to urea or other constituents, but probably ammonia is increased. The glycogen in the tissues is decreased, lactic acid is markedly increased; the available alkali of the blood is reduced and the alkalinity of the tissues is diminished. There is destruction of blood cells causing anæmia and fatty changes in different organs. Small necrotic areas are found in the liver and jaundice may occur. These effects are attributed to diminished oxidation of the tissues owing to the direct action of arsenic on the cytoplasm of the cells. The popular view is that the growth of young animals is stimulated by arsenic, but recent investigations have shown that this is not the case.

The change in nitrogen metabolism is very small. Excessive doses lead to loss of weight, fatty degeneration of organs and destruction of blood cells.

Fate in the body. Arsenic is absorbed readily even from the unbroken skin and mucous membranes. Poisoning may therefore result from the external use of arsenical cosmetic preparations. After hypodermic injection of large doses, diarrhoea may start within an hour.

Normal occurrence of arsenic in the body. It must be borne in mind that arsenic is a normal constituent of the human tissues, this was originally discovered by Gautier, (1899) and confirmed by Bertrand (1902-3) and others (1923-5). Arsenic present in the tissues normally

plays no part in their functions. In man it occurs especially in the thyroid gland (0.16 mgm.), in the thymus, brain, skin and hair; in the blood it has been estimated to be present to the extent of 0.3 mgm. per 100 c.cm. of a dried specimen. Arsenic to the extent of 0.3 mgm. has been found in 100 gm. of dried normal urine. It is found in milk after administration for medicinal purposes and through the milk it passes from the mother to the infant. Large amounts of arsenic are found in the lungs in pneumonia and cardiac disease. The arsenic occurring in the tissues normally is introduced with foods such as milk, eggs, fish, vegetable, wines, and also in drinking-water. It was estimated that in Paris every person receives about 7.66 mgm. annually. According to the Royal Commission of 1903 the quantity of arsenic in the food should not exceed 1/100 gr. per pound. Arsenic is invariably present in varying amounts in many medicinal agents. From the medico-legal point of view the quantity of arsenic normally present in the intestinal canal never exceeds 1/10 mgm.; larger quantities indicate poisoning or administration in the form of medicine.

Excretion. Arsenic disappears rapidly from the blood when injected and is fixed in certain tissues. It is chiefly found in the liver, kidneys, walls of the stomach and intestines, in the spleen and lungs. Much smaller quantities are found in the muscle and nerve tissue. With oral administration the main part leaves by the faeces; with hypodermic injection, by the urine. When arsenious acid or arsenites are given by the mouth or injected, they are excreted slowly, less than 20 per cent. appearing in the urine in the first twenty-four hours and a similar quantity in the faeces. After a single dose excretion of arsenic goes on for ten days, and after repeated doses it may continue for months. The arsenic retained is distributed in the tissues. It is also found in the hair and epidermis for months after its disappearance in the urine and faeces; traces may occur in other secretions.

Tolerance. If an animal is given daily doses of arsenic in gradually increasing quantities, after some months the usual lethal dose may be given without any symptoms of poisoning being produced. A similar tolerance can be established in man. The inhabitants of Styria consume arsenic in large quantities, as a general stimulant and to improve their complexions. As much as 7 or 8 grains (0.5 gm.) a day of the oxide are taken without apparent harm. It is said to produce intoxicating effects, stimulation of sexual and respiratory functions and a feeling of strength and well-being. Withdrawal does not cause any abstinence symptoms.

The phenomenon of tolerance to arsenic has not been satisfactorily explained. Some consider that the tolerance is limited to the intestinal epithelium, which no longer undergoes inflammation and necrosis under arsenic and absorbs less of this drug. Considerable quantities of arsenic, however, occur in the urine of arsenic eaters and therefore

absorption must occur. Another hypothesis is that an antitoxin is formed, while yet another explanation given is that non-ionisable organic compounds are formed in the body. Tolerance is sometimes acquired by the pathogenic protozoa, and arsenic-fast strains of trypanosomes have been experimentally produced. This apparent drug fastness has been attributed to two factors:—(1) deficiency of the host's tissues, (2) a nidus for the parasites in the tissues impervious to the drug.

Inorganic Arsenic compounds. All inorganic compounds of arsenic are very poisonous but metallic arsenic is insoluble in water and passes through the alimentary canal, for the most part unchanged and without exerting much action. It is probable that the activity is due to a compound of oxygen and arsenic appearing as an ion. The most important oxides are As_2O_3 , or As_4O_6 called arsenious anhydride commonly known as 'white arsenic' and As_2O_5 arsenic anhydride.

Arsenic and arsenious compounds. In *arsenic* compounds arsenic is pentavalent, and in *arsenious* it is trivalent. Trivalent arsenic (arsenites) is generally much more toxic for protozoa, bacteria and yeast cells than is pentavalent arsenic (arsenates). The pharmacological action of arsenic is said to be due to the negative ion AsO_3 of arsenious acid H_3AsO_3 , in which arsenic acts as a trivalent element. It is held that compounds in which arsenic is pentavalent, i.e., derivatives of arsenic acid H_3AsO_4 , are reduced to arsenious compounds in the tissues. Though when given by the mouth there is no very marked difference in the toxicity of pentavalent and trivalent compounds, when introduced by cataphoresis (nodal diffusion) the arsenates are much less caustic to the tissues than arsenites. This difference is also borne out by toxicity experiments on guinea-pigs when the arsenites are found to be much more lethal than the arsenates. The ratio of toxicity of arsenious to arsenic acids when given intravenously to rabbits is 6 to 1 and for the excised frog's heart 800 to 1.

Organic compounds of arsenic. The organic compounds in which arsenic is combined with carbon behave somewhat differently from the inorganic compounds. As long as they are present in an unchanged condition in the body, they do not exhibit the ordinary action of arsenic. This is because arsenic is present in a non-ionic condition. During the process of oxidation and reduction in the body, ionic arsenic is gradually split off and the action of arsenic is produced. For this reason the action is delayed and is mild. Both trivalent and pentavalent arsenic can be readily introduced into a large variety of organic molecules. The decomposition of organic arsenicals is, as a rule, slow and passes through many intermediate stages of simpler organic

molecules; a considerable portion is in all probability excreted from the body in organic form during this process. The organic compounds are much more toxic to pathogenic protozoa infesting the animal body and that is the reason why they are largely used in the treatment of diseases produced by these parasites. When these compounds are tested, *in vitro*, they produce little or no toxic effect on the parasites and they therefore require the co-operation of the tissues of the host to become effective.

Jackson and Smith (1918) studied the action of these compounds on the circulation. The pulmonary pressure was enormously increased after intravenous injection of arsphenamine probably due to the obstruction of the pulmonary circulation caused by the alkalinity of the solution and possibly also to the presence of an embolic precipitate formed in the vessels. The specific action of the drug on the musculature of the arterioles may be another factor concerned. The effects produced by neoarsphenamine are not so marked as, owing to its neutral reaction, intravascular agglutination of erythrocytes and precipitates are less likely to be formed.

Rolleston (1915) observed the effects of intravenous injections of salvarsan and neo-salvarsan on patients; the general effect of the injection was rather to lower, certainly not to increase, the arterial blood pressure.

Absorption and fate of the organic arsenic compounds. The rate of absorption varies with the different modes of administration of these compounds. After intramuscular injection, neoarsphenamine, which is less irritating than arsphenamine, is more quickly absorbed. Swift found that after intramuscular injection of arsphenamine in rabbits, some 30 to 40 per cent. of the arsenic was absorbed during the first week, about 50 per cent. by the end of the second week, while at the end of 6 weeks about 80 per cent. had disappeared from the muscles. In the case of neoarsphenamine, 80 per cent. of the arsenic had been absorbed during the first week and 90 per cent. by the end of the second, while only about 5 per cent. remained in the tissues at the end of six weeks. Arsphenamine or neoarsphenamine when given intravenously leaves the blood stream rapidly, at least three-fourths disappearing in a few minutes. Observations in animals show that after a single injection of one of the organic arsenicals, the arsenic is found most abundantly in the organs whose capillaries would mechanically absorb the flocculates. These organs are the liver, spleen and the lungs, the size of the former making it the principal storehouse of arsenic. The liver gets rid of arsenic by excreting it in the bile, where its concentration is forty times higher than in the blood; of all the tissues the bones retain arsenic the longest. The brain, spinal cord and the

nerves contain traces and in the cerebro-spinal fluid also it can be detected after intravenous injections.

Some authors have laid stress on the arsenic stored in the body forming 'depots' from which therapeutically active substances are being constantly produced. Kolmer has shown that arsenic stored in the liver after repeated injections of arsphenamine and neoarsphenamine is not therapeutically active. The stored arsenic may produce injurious effects; it is known that arsenoxide is toxic to the tissues, but tissues can oxidise it to non-toxic products. The therapeutically inactive pentavalent arsenic may be injurious to tissues, and anything which hinders its excretion increases its toxicity without enhancing its therapeutic effects.

Excretion of organic arsenicals. Pentavalent compounds. After a single dose of these compounds, the arsenic is excreted promptly, and mostly in the urine. With continued administration, the excretion is prolonged, the greater part leaving within 3 days, but traces continue for 3 weeks; the effect is cumulative. A small part is excreted by the faeces. A large part of the arsenilate remains unchanged in the blood and tissues. The excretion of atoxyl commences early; as about 85 per cent. of the dose injected is excreted in the urine within 24 hours. The reason for this rapid excretion is that pentavalent arsenic is not fixed in the body cells. The inorganic arsenates are rapidly reduced in the body to the trivalent arsenites and in this form the arsenic is fixed in the tissue, but compounds, *e.g.*, atoxyl and tryparsamide, are reduced much more slowly and are therefore rapidly excreted by the kidneys.

Trivalent compounds. Salvarsan is excreted very slowly, the maximum amount of arsenic occurring in the urine being about 1.0 per cent. in 24 hours and a somewhat larger amount occurs in the faeces, the total amounting to about 3 per cent. The drug is excreted more slowly after intramuscular than after intravenous injections. Salvarsan is insoluble in neutral media and therefore cannot exist in the blood in true solution, but probably as a colloidal suspension. About 80 per cent. leaves the blood in five minutes after an intravenous injection, but small quantities circulate in the blood unchanged for 12 hours, and traces of arsenic can be detected in the blood for 12 days. The greater portion of the drug is fixed in the liver, where it forms a depot, from which it is released slowly. Neo-salvarsan disappears from the blood slightly more rapidly than salvarsan and is said to be excreted more rapidly.

It has been pointed out that during their excretion inorganic arsenic compounds set up cloudy swelling of the epithelial cells, fatty degeneration and hyperaemia of the sub-mucosa of the gastro-intestinal tract; the kidneys are affected in the same way. Organic arsenicals produce the same changes though not to such a marked extent. Arsenic is also eliminated by the skin; it is known to have a marked affinity

for the epithelial cells and it is probable that the production of ex-foliative dermatitis can be accounted for in this way and the presence of peripheral neuritis may further facilitate its production. In cases of organic arsenicals also, traces of arsenic are excreted in the saliva and milk.

It will thus be seen that probably only a portion of arsenic, in whatever way it is administered—by the mouth, subcutaneously, intramuscularly or intravenously—can exert therapeutic effects.

Classes of organic arsenic compounds. The starting point of all these are two acids, known as arsinic acid (trivalent) and arsonic acid (pentavalent). Arsinic acid is a dialkyl or diaryl derivative of arsenic acid, *e.g.*, cacodylic acid or dimethyl arsinic acid $(\text{CH}_3)_2\text{AsO.OH}$, or diphenyl arsinic acid $(\text{C}_6\text{H}_5)_2\text{AsO.OH}$. Arsonic acid indicates arsenic acid $\text{AsO}(\text{OH})_3$ in which one hydroxyl is replaced by an organic radicle. An arsonate is a salt of this acid.

(A) *Aliphatic (or fatty) series.* The effects of cacodylic acid are essentially those of the inorganic arsenic, to which it is partly reduced in the body. Sodium cacodylate is probably such a stable compound that it is broken down in the tissues to a very small extent. Very large doses can be given without producing any therapeutic, much less any toxic effect; it is excreted in the urine mostly unchanged but small quantities may be oxidised. Sodium cacodylate can also be given intravenously.

Calcium cacodylate, iron cacodylate, guaiacol cacodylate, magnesium cacodylate and strychnine cacodylate are some of the other compounds used either by the mouth or intramuscularly. They have been given in tuberculosis, diabetes mellitus, pernicious anaemia, exophthalmic goitre, leprosy, malaria, chorea, skin affections such as psoriasis and also in syphilis with varying results.

(B) *Aromatic (Benzol) series.* The development of this series of compounds is due to the efforts of Paul Ehrlich to obtain drugs which would destroy the organisms producing disease in the body. Clinical experience has already shown that protozoal infections, malaria, syphilis and amoebiasis may yield to specific drugs like quinine, mercury and ipecacuanha respectively, whilst no bacterial infection of man has been suppressed *in vivo* by chemicals. Evidently bacteria are more resistant, so that protozoa offer the more promising approach.

The starting point of Ehrlich's investigation was atoxyl which is the sodium salt of p-aminophenyl arsonic acid also known as arsenilic acid. His efforts were directed towards separating the antiparasitic portion from the toxic portion of the molecule. By multiplicity of changes, synthesis and experiments on thousands of infected animals, he endeavoured to find which atoms or groups of atoms and what grouping in the molecule increased the affinity for the parasites and reduced the toxicity to the cells of the host most. Substitutions

in the NH_2 group may cause profound differences in the effects of the compounds—sometimes an increase and sometimes a decrease in the therapeutic effect. If acetamide is introduced into the NH_2 group, tryparsamide is formed which is ten times less toxic than arsanilic acid.

A compound, sodium acetyl-p-aminophenylarsonate, also known as arsacetin or acetylatoxyl was prepared and this was followed by a number of other compounds. While these combinations proved useful in syphilis and in protozoal diseases they were not devoid of their toxic effects on the host. Ehrlich, from his experiments, concluded that these pentavalent arsenic compounds such as atoxyl and its derivatives, were really inactive in themselves and only acquired activity when they were changed into trivalent arsenic. This led him to seek for organic compounds in which arsenic was present in trivalent form. Many of these compounds were prepared of which arsenoxide, arsenophenyl glycine, etc., are examples, and eventually salvarsan and neo-salvarsan were discovered. These are very active compounds but during the last decade some powerful pentavalent compounds have also been prepared.

The aromatic compounds of arsenic may be divided into:—

(a) *Those in which arsenic is pentavalent. Arsanilic acid derivatives:*

Atoxyl is the monosodium salt of p-aminophenyl arsonic acid or p-arsanilic acid. It is also known as *arsamin* or *soamin*.

Arsacetin or sodium acetyl-p-aminophenylarsonate is tolerated in three to ten times as large doses as atoxyl. Its curative action against diseases caused by trypanosomes and spirochaetes is not marked.

Carbarsone or 4-carbamino-phenyl arsonic acid was first prepared by Ehrlich in 1909, but has only been recently used in the treatment of amoebic dysentery.

Since the war the study of pentavalent compounds has been keenly pursued. *Tryparsamide* (sodium-n-phenyl-glycinamide-p-arsonate) was discovered at the Rockefeller Institute, New York. Fournneau and his colleagues at the Pasteur Institute, Paris, produced a series of compounds of which *Fournneau 270* (Sodium-4-acetyl-amino-2-hydroxyphenylarsonate) and *Stovarsol* (Sodium-8-acetyl-amino-4-oxyphenyl arsonate) are well known. *Acetylarsan* is a simple derivative of stovarsol. They threw light on the relationship between chemical constitution and trypanocidal action. *Treparsol* or 3-formyl-amino-4-hydroxyphenyl arsonic acid is another compound which behaves like stovarsol. Both these compounds can be given by the mouth.

Etharsanol or monosodium salt of p- β -hydroxyethyl-amino-phenylarsonic acid and *Proparsanol* or monosodium salt of p- γ -hydroxypropyl-amino-phenylarsonic acid contain about 20 per cent. of arsenic. *Etharsanol* is an effective trypanocide experimentally and is on trial in man.

(b) *Those in which arsenic is trivalent.* *Arseno-benzene derivatives*:—These compounds are said to have a di-benzol or arseno-benzene nucleus coupled together by two trivalent atoms of arsenic. The nucleus itself is of no therapeutic value and is of interest only because it is the parent substance of salvarsan and neo-salvarsan (arsphenamine, neoarsphenamine, etc., in the United States).

Various substances were prepared by reduction of arsenic acid. *Arsenoxide* or 3-amino-4-hydroxy-phenyl-arsenic oxide is a toxic compound, its minimum lethal dose for white rats being 21.8 mgm. per kilo. body weight; *arsenophenyl-p-glycine* in the form of its disodium salt has a minimum lethal dose of 197 mgm. per kilo. for white rats. This compound was called 'spirarsen,' 'spirarsyl' or No. 418 of Ehrlich's series and has got trypanocidal and spirochaeticidal properties in doses much smaller than its M.L.D.

Salvarsan is No. 606 of Ehrlich's series; it is the dihydrochloride of dioxy-diamino-arseno-benzene. It is also known as *arsphenamine*, *kharsivan*, *arsenobenzol*, *arsenobillon*, etc. *Arsphenamine diglucoside* is known as *stabilarsan*.

Neo-salvarsan is No. 914 of Ehrlich's series and is a condensation product of salvarsan. It is sodium-3:3'-diamino-4:4'-dihydroxyarseno-benzene methylene sulphonylate and is derived from salvarsan by introduction of a methylene sulphonic group into one of the amino groups. It is known as *neokharsivan*, *neoarsphenamine*, *novarsenobenzol* and *novarsenobillon*.

Silver sodium salvarsan and *silver neo-salvarsan* have a high chemotherapeutic index. The maximum tolerated dose for silver salvarsan is 167 mgm. and for silver neo-salvarsan is 278 mgm. per kilo. as compared with 870 mgm. of neo-salvarsan.

Metarseno argenticum is a compound of silver with metarsenobillon, (formaldehyde bisulphate derivative of arseno-benzene). Recently, compounds of salvarsan with bismuth have been introduced.

Sulpharsenol or sulpharsphenamine is disodium dihydroxy-diamino-arsenobenzene-*n*-dimethylene-sulphonate. It is also known as *sulpharsenobenzene*, *kharsulphan*, *myosalvarsan*.

Galyl (No. 1116 of Mouneyrat's series) is Tetraoxy-diphosphamino-diarsenobenzene and more recently *neo-galyl* which is the sodium salt of galyl has been prepared.

Ludyl (No. 1151 of Mouneyrat's series) is Phenyldisulphamino-tetraoxy-diamino-diarsenobenzene.

Luargol is 3:3'-diamino-4:4'-dihydroxy arseno-benzene-silver bromide-antimonyl-sulphate. A number of other co-ordination compounds with gold, mercury, copper and antimony have been prepared but they appear to have no superior therapeutic properties.

CHAPTER XXVIII

THERAPEUTIC USES OF ARSENICALS

Arsenious oxide has been used as an application in malignant diseases, its action being of slow caustic nature. Owing to the depressing action of arsenic on the nerves, it has been used in neuralgias, especially of the periodic type and in chorea. In rheumatism and asthma also it has been used and its administration in chronic skin diseases such as psoriasis, pemphigus, lichen and leprosy is well known. Here it probably acts by improving the nutrition of the skin. Arsenicals have also been used in infections with anthrax, *B. coli*, streptococcus and staphylococcus, with encouraging results. In puerperal septicaemia, erysipelas, pulmonary gangrene, gonorrhoeal arthritis, leprosy, broncho-spirochaetosis, typhus fever, and cancrum oris, they have been tried with encouraging results. The bactericidal properties of arsphenamine and neo-arsphenamine on the organisms of anthrax, glanders and swine erysipelas have been the subject of many papers. When injected into animals and the human body, arsenicals confer on the blood peculiar bactericidal properties which are retained for a considerable time. This will be seen from the fact that the serum of patients after injection of arsenicals exerts a bactericidal effect upon staphylococci and hæmolytic streptococci. The arsphenamines, especially silver arsphenamine, have a toxic action on the leucocytes, but they have considerably stronger affinity for certain microbes, such as pneumococci and hæmolytic streptococci than for leucocytes. In such infections sulpharsphenamine is now preferred in 0.3 gm. doses. The following scheme is usually followed: first two doses at an interval of 6 hours; 3rd dose after 18 hours; 4th after 24 hours; 5th after 48 hours; 6th after 3 days, 7th after 4 days and 8th after 5 days.

Anæmia. Bramwell (1875) first announced that arsenic was beneficial in the anæmia of the pernicious type. Since then Fowler's solution and other preparations of arsenic have been

very largely employed in this disease and also in such conditions as leukaemia. Unfortunately the improvement produced is of a very temporary nature. In other anaemias arsenicals are said to act (1) by destroying the parasitic agent responsible for producing the condition, (2) by stimulating the bone-marrow and other blood-forming tissues, (3) by increasing the resistance of erythrocytes against hæmolytic agents, (4) by generally improving the metabolism. Excellent effects are produced by arsenicals in anaemia of syphilitic origin. Kolmer (1925) observed that arsphenamine and its substitutes cannot be regarded as curative agents, in a strict sense, for the non-syphilitic anaemias. They however improve the condition and small doses of neo-arsphenamine (0.1 to 0.3 gm.) give better results than inorganic arsenic by the mouth.

Helminthiasis. (See Part II, Helminthic Diseases). Arsenicals have been tried against some of the helminthic infections such as bilharziasis but have not proved very successful. McNerthney (1916) and Nieto (1924) recorded apparently successful results with 2 or 3 intravenous injections of neo-salvarsan in doses of 0.45 gm. each against trichinosis.

Some of the trivalent organic arsenicals are said to have a filaricidal effect, but this is doubtful. They do sometimes cause disappearance of microfilariae from the blood and chyluria is often benefited by tryparsamide. Neo-salvarsan has been used in the treatment of guinea worm.

Malaria. Inorganic compounds of arsenic such as arsenious oxide or arsenites have been used to reinforce the action of quinine in malaria, especially in those cases in which cachexia is present. Some authorities consider arsenicals to be of value in acute cases of the disease and they are supposed to act (1) by destroying the parasites which have a low susceptibility to quinine and (2) by increasing the vitality of the tissues generally, and particularly of those concerned in the formation of blood. They are said to cause disappearance of the parasites of benign tertian type though they have no effect on the subtertian parasites. This also does not appear to be the case, but there is no doubt that arsenic compounds do help the action of quinine.

The organic arsenicals on account of their trypanocidal and spirochæticidal properties were tried in the treatment of malarial fevers, and it was shown that injections of salvarsan and neo-salvarsan may stimulate cases of chronic malaria into activity, sometimes with fatal results. In some cases this reaction has been used as a provocative method for finding the parasites in the blood. This dislodging of the parasites is probably caused by the vasodilating action of these compounds. Some authorities lay stress on the arsenicals being useful adjuvants to quinine, especially in chronic quartan and tertian infections, while others say that they may be actually harmful. In malaria of birds, arsenicals have no effect and tend to lower the resistance of these animals. Stovarsol in 1.0 gm. doses by the mouth several times a day is said to be efficacious in malaria.

Clinical experience shows that organic arsenicals such as salvarsan, neo-salvarsan, and stovarsol possess only slight parasito-tropic properties against the plasmodia of malarial fevers of man; they have little or no effect on the sexual forms. In acute malaria they cannot be recommended. In chronic malaria the arsenicals tend to bring the parasites into the blood where they are exposed to the action of quinine. Further, they improve the anæmia and generally stimulate the metabolism and nutrition. Injections of soamin are often useful.

Trypanosomiasis. Bruce (1895) first used the arsenical preparations in the treatment of the trypanosome infections of animals 'nagana' and 'surra.' Ehrlich and Shiga (1904) studied the effects of atoxyl and other substances on trypanosomes *in vitro* and Thomas (1905) showed that atoxyl cured laboratory animals infected with a number of different species of trypanosomes. Koch (1907) employed atoxyl in the treatment of sleeping sickness in Africa and although the first results were good, relapses occurred and optic atrophy was often produced. Tryparsamide and Fournieu 270 were introduced after the War and this was a further step in the treatment of this disease but the hope that the disease could be eradicated has not been realised.

Attempts to get compounds which may have trypanocidal activity, when given by the mouth, have also not been successful. No compound

has been discovered which will penetrate the central nervous system to a greater degree than tryparsamide. Etharsanol (p- β -hydroxyethyl-aminophenylarsinic acid) and Proparsanol (p- γ -hydroxy-propylamino-phenylarsinic acid) differ little in their chemical composition from tryparsamide. The former contains 20.32 per cent. of arsenic and is toxic, but the latter has 20.68 per cent. of arsenic and has a similar action to tryparsamide. Etharsanol given intravenously is very rapidly excreted and therefore can be given in maximum tolerated doses. In man 15 per cent. was excreted in 5 hours, and 91 per cent. in 4½ days. In rats and rabbits infected with *T. brucei*, *T. equiperdum*, *T. equinum*, *T. lewisi*, and *T. rhodesiense*, etharsanol is an effective drug. Rabbits could even be cured when, as shown by lethargy and paralysis, the central nervous system was affected; on analysis, brain substance was found to contain large quantities of arsenic. The drug has so far been tried only in a few human cases.

A number of other arsenic acid derivatives have been tested on mice infected with *T. equiperdum*. Some of these compounds resemble stovarsol in action while others resemble tryparsamide. Some of the benzisoxazinearsinic acid derivatives are just as effective in animals when given by the mouth as when given by injection. Some of these compounds have been tested in human trypanosomiasis, but they produce diarrhoea and vomiting without any amelioration of symptoms. Stovarsol by the mouth is ineffective. A large number of derivatives of phenylarsinic acid have also been tested. Acetylarsan in doses of 0.75 gm. each, given subcutaneously at intervals of one week till 12 gm. are given, improved the general condition and produced a decrease in the lymphocytosis in the cerebro-spinal fluid. The results were inferior to tryparsamide. Fourneau 269 and 417 have also been tried with variable results.

The trivalent compounds of arsenic are not so effective in this condition. The pentavalent compounds act more efficiently on the parasites in the blood and cause their prompt disappearance, but have comparatively less effect on those which have infected the lymphatic glands and apparently they do not penetrate in sufficient concentrations to destroy the organisms present in the central nervous system. The supply of the parasites into the blood stream is, therefore, constantly renewed from these foci; but there is no doubt that they ameliorate symptoms and prolong life.

Jamot (1926) treated 50,000 patients with atoxyl, and found that treatment of the population with atoxyl on a large scale failed to eradicate the disease. He also tried tryparsa-

mide and testified to the beneficial effects produced by this drug in advanced cases of the disease. In the early stages when the cerebrospinal fluid is not infected with the parasites, atoxyl, which is cheaper, should be prescribed. It is given in doses of 1.0 to 1.25 gm. to adults, the doses being given at intervals of 10 to 16 days, a series of six injections constituting a course. In the second stage moderate doses produced slight clinical amelioration, but the effects were of short duration and after 4 or 5 months the patients had relapses. In advanced stages of the disease when the cerebrospinal fluid contains leucocytes and albumin, tryparsamide is recommended. Whenever there is doubt about the stage and when lumbar puncture cannot be done, tryparsamide which gives better results in both stages should be tried.

Dengue. This disease is sporadic in many parts of India but has occasional epidemic exacerbations. The disease is carried by some species of mosquito, *Culex fatigans* in Syria and *Stegomyia fasciata* (*Aedes ægypti*) in Australia and other countries. Clinically it resembles phlebotomus fever; the blood of early cases of both phlebotomus fever and dengue is infective if inoculated in susceptible persons even after passage through a Berkefeld filter, indicating an ultra-microscopic stage of the causative organism. The disease can also be transmitted to guinea-pigs. Spirochaetes are probably not the causal organisms. Novoarsenobenzol in 0.45 gm. doses has been tried in this condition but has little effect. Pirot (1927) treated 17 cases of dengue with intramuscular injections of 6 gm. of sulpharsphenamin on the first three days of the disease. In nine cases there was a marked lowering of the temperature and decided amelioration of the joint and bone pains. Relapse was also prevented in the other eight, the fever was of shorter duration than in the controls, and although there were relapses, they were not as severe as in the untreated cases. Treparsol has been tried by the mouth in 15 grain doses (1.0 gm.) per diem for the first 3 days. Although the disease was not cut short there was amelioration of symptoms. The best results were obtained by hypodermic injection of 3 c.cm. of acetylarsan. If given about the second or third day it is said to abort the fever.

Intestinal protozoal and other infections. Musgrave (1922) has shown that chronic diarrhoea with intermittent exacerbations and other digestive disturbances occur in infection with *Giardia intestinalis* and trench-diarrhoea so common during the Great War was also attributed to this organism. In children, lamblasis is said to produce wasting, retardation of growth, etc. Salvarsan, neo-salvarsan and stovarsol by the mouth have offered more encouragement in the treatment of this condition than any other drug. It has been shown that after an intravenous injection of neo-salvarsan, arsenic appears in the duodenal fluid in $1\frac{1}{2}$ hours but the flagellates remain at first active. The arsenic reaction is increased after about 2 hours and the flagellates become motionless. Later, arsenic reaction is absent but flagellates disappear altogether. Stovarsol in doses of 0.5 gm. per day by the mouth has been used in chronic amoebiasis and in the treatment of lamblia as well as trichomonas infestations. *E. coli* and *E. nana* are said to disappear from the stools rapidly. Carbarsone has recently come into use in amoebiasis and is stated to be less toxic than stovarsol.

Diseases produced by spirochaetes or spirilla or spironema.
Relapsing fever. This disease is met with in Eastern Europe and North Africa, India and the Southern United States. *Sp. duttoni* is the causal organism in the Central African variety which is practically the same organism as *Sp. recurrentis*. This infection is transmitted by the tick *Ornithodoros moubata*. Monkeys can be readily infected and lice are the carriers of infection in man. The fever varies much in severity, the first attack usually lasts six days, and relapse occurs after seven or more days, intermissions being few in number. An enormous mortality occurred in Russia during the War and in subsequent famines. Localised outbreaks occur in different parts of India during April and May. *Spironema berberium* in Persia is probably transmitted by the bite of the tick *O. tholozani* or *miana*. The ticks or lice become infected by biting the patients suffering from the disease. The spironema become granular in their stomachs in three hours and disappear in twenty-four hours and after 10 days appear in their hæmolymph in which they persist. The fluid which escapes from the louse

after crushing is highly infective. Infections with spirochaetes occur in squirrels in China and India.

In the early work of Hata and Ehrlich on the organic arsenicals, mice infected with *Sp. obermeieri* were used. The inorganic compounds have little or no effect on this spirochaete infection and even the organic compounds have a less powerful effect on these organisms than on the trypanosomes. Recent experiments with mice infected with the spirochaetes of relapsing fever show that injections of salvarsan cause a rapid disappearance of the organisms from the blood but they still persist in the brain. Though a single injection may bring about an apparent cure, the spirochaetes may still remain active in the central nervous system. Strains of relapsing fever spirochaetes differ in their resistance to arsenic. Clinically, encouraging results have been obtained in the treatment of relapsing fever, 0.2 to 0.3 gm. of arseno-benzol compound producing a sudden fall of temperature in a few hours; spirochaetes disappear from the blood and the patient appears to be cured. The fall of temperature is accompanied by rigors, which are said to be produced by the liberation of endotoxins from the parasites killed by the drug. Full and repeated doses have to be given before the parasites can be eradicated from the brain. Neo-salvarsan in doses of 0.45 to 0.6 gm. produces excellent results in relapsing fever. As a routine 7 to 8 doses are necessary, one being given every week, and cases treated at the commencement of the illness respond much more quickly than patients who have had relapses. One and a half gm. of stovarsol given by the mouth on two successive days is said to produce disappearance of the spirochaetes from the blood in 6 to 36 hours and to prevent relapses. The drug has also been used prophylactically.

Rat-bite fever. Rat-bite fever is caused by *Spirillum minus* which is a spirillum of rigid structure conveyed to man by the bites of rats, cats and weasels which are infected with the parasites of the disease. The infection is characterised by an acute febrile reaction with a local disturbance at the site of infection and in some cases cutaneous eruptions. The organisms appear in the blood stream usually seven days after inoculation and persist for several months afterwards. The incubation period

of the disease is 5 to 10 days or more. Fever comes on with rigor and malaise and ends by crisis about the sixth or seventh day. Relapses frequently occur. One or two injections of neo-salvarsan suffice to bring down the temperature and cause disappearance of the roseolar rash. The injections should be given early in the course of each spell of fever rather than at the end of the paroxysm or in the fever-free period. In severe cases 0.6 gm. to 0.9 gm. at weekly intervals for about 6 weeks is necessary. Oxy-acetyl-amino-phenyl arsinic acid has been tried in rabbits infected with rat-bite fever. The prophylactic use of arsenic has also been found successful.

Syphilis. This disease is produced by *Spirochaeta pallida* now more correctly called *Treponema pallidum*. It is acquired by contact, commonly sexual intercourse or is transmitted through the mother. The name 'syphilis' first appeared in 1530 in a poem, 'Syphilus' being the name of the infected hero. It is essentially a parasite of the lymphatic system and tissues. The organism is extracellular in the body and occurs practically in all the tissues particularly the cardiovascular, lymphatic and nervous tissues. The introduction of organic arsenical compounds marked a new era in the treatment of syphilis. They produce most remarkable results on the lesions produced by the disease and the dictum 'once a syphilitic always a syphilitic' is gradually giving way to the belief that the disease is curable. It is probably one of the transformation products which destroys the parasites and prevents the development of new generations, for *in vitro* their action is not very powerful, and the effect is enhanced by adding an extract of liver. It was hoped at first that a single injection would suffice to destroy all spirochaetes and realise the ideal of '*therapia sterilisans magna*' but though this hope has not been entirely fulfilled, very often a single dose causes disappearance of spirochaetes and the Wassermann reaction becomes negative; but in a large majority of cases spirochaetes reappear and the symptoms develop again. This is due to the fact that the first injection suffices to kill a large number of parasites, but a few which survive reinfect the tissues and develop a certain degree of tolerance to the drug. The drug should be injected repeated-

ly at regular intervals while vigorous mercurial treatment at the same time is recommended. Injections should be started as soon as the diagnosis is confirmed and before the parasites have had time to reach inaccessible positions in the tissues. Within two weeks of the initial lesion it may, if given in repeated doses, produce a complete cure. In patients with primary and secondary manifestations like ulceration of the penis, mucous patches in the mouth and throat, arsenicals have a marvellous effect in clearing up the lesions. Their power to produce a perfect cure diminishes as each week passes, and after secondary symptoms have appeared, the question of cure in the true sense becomes problematical. One of the important results of treatment is that the patient becomes relatively innocuous as far as transmitting the disease to others is concerned. The arsenicals also shorten the contagious period of the disease and afford a sure protection against the development of tertiary and quarternary manifestations. It should be borne in mind that these compounds should be given in adequate doses ; too small doses not only fail to cure but are believed to produce a resistant strain of spirochætes. Stovarsol by the mouth is said to be effective against syphilis but this needs further confirmation.

Syphilis of the central nervous system. There has been considerable difference of opinion regarding the presence of arsenic in the cerebro-spinal fluid after injections of the arsenicals. The exact origin of this fluid is not known, but it is probably a form of secretion of the choroid plexus and ependymal cells which effectually prevent the passage of most drugs into it. Hexamine, chloroform, etc., may pass into it, but from the point of view of drugs used in the treatment of syphilis, mercury has never been found in this fluid and iodine has not even been detected after intravenous injection of iodides. It is probable that in disease of the meninges these substances may pass into the cerebrospinal fluid.

Lately much work has been done to determine the penetrability of organic preparations of arsenic into the cerebrospinal fluid. The experiments consisted of both quantitative estimation by chemical methods as well as biological methods in

which the effect on *T. brucei* present in the central nervous system was determined. The conclusions are as follows:—The penetration of arsenic into the cerebro-spinal fluid following intravenous injections of arsephenamine, neoarsphenamine, silver arsphenamine, etc., is very small and these drugs have a relatively low effectiveness in cerebral affections.

Sulpharsphenamine or sulfarsenol is said to be the most effective of the arseno-benzene derivatives in this respect and possesses superior therapeutic power in syphilis of the central nervous system to any of the other arsenicals. Greater therapeutic effect can be produced by giving large doses of arsenicals at longer intervals. Tryparsamide has also been recommended in the treatment of neuro-syphilis and often the patients show signs of distinct clinical improvement. Eight consecutive weekly injections are recommended in a course, which may be repeated at suitable intervals.

Arsenicals differ from mercury in the greater rapidity of their action. This is due to the fact that sterilising concentration of mercury can be reached only after several days, while given by the intravenous route salvarsan acts in a few hours. The disadvantage of the arsenicals is that most of them are excreted within 3 days and the surviving parasites multiply unretained. A combination of the two therefore appears to be the best; the arsenicals have supplemented rather than replaced the older drug. A number of organic compounds containing both arsenic and mercury were introduced but they proved to be disappointing. A course of iodides at various stages of the treatment is decidedly helpful. Probably it acts by breaking down the fibrous tissue which surrounds the spirochaetes in the lesions.

Framboesia. Yaws is one of the most widespread tropical diseases. It is prevalent in Africa and Asia. In India it occurs in Assam and parts of Bihar, in Ceylon and Burma. The causal organism is *Treponema pertenue* which is indistinguishable morphologically from *T. pallidum*. Serum reactions like the Wassermann test and Sachs-Georgi reaction are also positive in yaws. Rabbits can be experimentally infected with the organisms of yaws. *T. pertenue* is not as

virulent as *T. pallida* and hence experimental yaws is more readily influenced by arsenicals than syphilitic infections.

Nichols (1911) was the first to discover the curative effect of salvarsan in yaws in rabbits. Clinically the arsenical compounds produce a wonderful effect in yaws in man. The prompt effect produced by a single injection is such that it is often difficult to get the patients to realise the necessity for continuing the treatment to ensure permanent effects. After two or three injections the long-standing lesions disappear and the patient is usually cured. Stovarsol by the mouth in 0.5 to 1.0 gm. doses for 7 to 10 days has been used with good results. Treparsol has also been used orally with good results; 4.25 to 14.75 gm. are necessary to produce a cure. In Western Samoa, where yaws is very prevalent, the standard treatment followed is to administer three doses of a trivalent compound intravenously at one week's interval.

Although the introduction of arsphenamine has revolutionised the treatment of yaws, real cure is not always attained. The secondary eruptions undoubtedly disappear, but many cases pass into a latent condition. A course of six injections of 0.6 to 0.75 gm. of neoarsphenamine has been recommended at intervals of a week or ten days to prevent relapses. With three injections of 0.6 gm. there is a relapse rate of 10 per cent. within 8 months. The serum reaction remains positive in many cases. Intramuscular injections of sulpharsphenamine are effective, 2 to 3 injections being required. Some cases are resistant to the action of neoarsphenamine (see also bismuth).

Vincent's angina is generally regarded as being due to a spirochaete and the *Bacillus fusiformis*. Injections of arsphenamine are very useful in this condition. The influence of arsenicals on the saprophytic spirochaetes of the mouth is very doubtful and the role of spirochaetes in the production of bronchitis is highly uncertain. In cases of pulmonary gangrene associated with spirochaetes in the lungs, excellent results have been obtained by injection of arsphenamine.

Other conditions. In cerebro-spinal fever, injections of arsenicals may produce improvement. Phagedenic ulcers of the mouth improve by painting with stovarsol solution. In veteri-

nary medicine they have assumed great importance and besides diseases of protozoal origin they are also used in the treatment of contagious diseases of the lungs especially in horses. Against anthrax and glanders they are also said to have a beneficial effect.

The action and therapeutic uses of some of the most important members of the group will now be discussed in detail.

MODES OF ADMINISTRATION

Local application. One in 1000 solution of salvarsan and neo-salvarsan exert spirochaeticidal effects on *T. pallidum* and *T. pertenue* in chancres, mucous patches and other syphilitic and framboesial ulcers; some of the other spirochaetal affections such as Vincent's angina are also benefited. Under the microscope, 1 in 1000 solution destroys the motility of the spirochaetes immediately. A one per cent. ointment of arsphenamine applied within an hour of exposure, or powders applied to ulcers, are effective in preventing infection; they do not produce irritation.

Oral and rectal administration. Salvarsan was first tried by Hata in a human case at the Imperial Institute of Tokyo. Oral administration was tried and although there were no toxic symptoms except vomiting and diarrhoea the therapeutic effects were very feeble. Kolmer (1912) and others have shown that arsphenamine is absorbed when given by the mouth but produces symptoms of gastro-intestinal irritation. To Rabaut belongs the credit of introducing arsenical compounds by the mouth in the treatment of amoebic dysentery and pentavalent compounds like stovarsol and treparsol are now sold in tablet form and are largely used with satisfactory results.

The rectal method has been tried with salvarsan but is even inferior to the oral route. After administration of 0.6 gm. per rectum, only traces were found in the blood while the urine gave a negative test for arsenic. Arsenobenzol suppositories containing 0.1 gm. each have been prepared and are used in the treatment of diabetes mellitus.

Subcutaneous and intramuscular injection. Subcutaneous and intramuscular injections have been tried in aqueous

solution, olive oil or liquid paraffin but salvarsan tends to deposit locally and gives rise to pain and swelling even when the solutions are carefully neutralised or mixed with olive oil (10 per cent.) before injection. The rate of absorption from the muscles depends primarily on the degree of injury to the tissues; neo-salvarsan, which is neutral in reaction, produces less irritation than salvarsan, which is acid, and is therefore absorbed 5 to 6 times more quickly. It has however been found locally for as long as 36 days or even later, and repeated injections may cause cumulative poisoning. Kolmer (1926) conducted experiments upon the rate of absorption of arsenicals and found that as compared with neo-arsphenamine in the same dose and concentration, the absorption of sulpharsphenamine was generally but not always considerably more rapid and likewise produced less tissue injury. It is the only one of the trivalent arsenicals which can be safely given by this route and produces the therapeutic effects desired. The advantages of the subcutaneous and intramuscular routes are that acute toxic reactions are much less common though they are not altogether eliminated; the disadvantages are that local reactions are produced. The pentavalent compounds such as atoxyl, tryparsamide, stovarsol, as a group produce less local reactions than trivalent compounds.

Intraspinal, intraperitoneal and intrapleural methods. Even when well diluted with spinal fluid, the arsenical compounds given in the spinal canal produce considerable irritation of the cord causing severe shooting pains; the respiratory and cardiac centres are not affected. This form of medication is as a rule not employed. The safest medicine for subdural injections is the serum of patients who have recently received injections of arsenicals. As intraperitoneal and intrapleural injections produce irritation they are not recommended.

The administration of most of these compounds by ordinary methods is not very effective in cerebro-spinal syphilis, as very little of the drug passes into the cerebro-spinal fluid. The plan of doing a lumbar puncture after injection so as to set up a negative pressure and an ultrafiltration through the choroid plexuses, has been recommended. This is absolutely harmless and said to produce beneficial effects.

Intravenous route. The intravenous method is the one usually adopted. The disadvantage of the intravenous method is that the drug is rapidly eliminated and consequently the period of spirochæticidal activity is short. Besides, the technique is more difficult and the incidence of acute toxic reactions is higher, due to factors inherent in the drug itself or in its solvents. The main advantage is the freedom from pain and disability when intravenous injections are properly given. The intravenous route is preferred in acute early stages of syphilis for rapid destruction of spirochætes in lymph, blood, and tissues; in later stages however when most of the organisms are fixed in the tissues, the intramuscular and subcutaneous routes are preferred by some, because the absorption and excretion rates are reduced and spirochæticidal effects are enhanced. Some give intravenous and intramuscular injections alternately. After intravenous injections the reticulo-endothelial cells of the spleen, liver and lymph glands become swollen, and granules of the compounds can actually be demonstrated in them. After very large doses of neo-salvarsan the granules can be demonstrated in the capillary endothelium, the intestine and the salivary glands as well.

The elaborate technique of preparation, neutralisation and injection of salvarsan is no longer necessary with neo-salvarsan and other allied compounds, as they have a neutral reaction when dissolved in distilled water. The temperature of the solution should not exceed 22°C. or 71°F. Slight febrile reaction generally occurs after the first injection; if this reaction reappears in the course of the treatment (*i.e.*, on subsequent injections) it is a sign of intolerance. The rate of injection of these compounds is of importance. A concentrated solution injected slowly is as well borne as a dilute solution injected rapidly; but if injected rapidly they both produce a higher incidence of toxic reactions. With solutions of neo-salvarsan, sulfarsenol and tryparsamide the importance of rapid injections is not so great as with those of salvarsan, as the former being neutral in reaction do not produce intravascular reactions such as hæmolysis, agglutination and precipitation. The kidneys should be

carefully watched and the urine tested for albumin before each injection. Sometimes the rubber tubing, through which solutions pass, may produce toxic symptoms; this is due to the inferior quality of rubber and boiling does not prevent such effects.

A study of the various vehicles for the injection of the novarseno-benzol compounds has been made. In order to get the quickest and best results in the treatment of syphilis, the tendency is to give these preparations in doses as large as possible and to shorten the interval between courses. This unfortunately often produces toxic and sometimes fatal results. In order to avoid angioneurotic symptoms, dermatitis and other complications, a number of diluents other than saline were tried. Blood serum, glucose, saccharose, calcium chloride, egg albumin, and gum, have all been tested. Neo-arsphenamine dissolved in 5 to 20 c.cm. of a 6 per cent. aqueous solution of caesium eosinate in place of distilled water is said to prevent anaphylactic symptoms. It is an expensive compound and if not pure it is toxic. Of all these, glucose appears to be the best as to some extent it prevents oxidation. Thirty c.cm. of a 30 per cent. solution of glucose, given intravenously in conjunction with neo-arsphenamine is said to increase the efficacy of the latter. Gelatine, blood serum and calcium chloride have proved effective in some cases.

CHAPTER XXIX

ORGANIC COMPOUNDS OF ARSENIC

ATOXYL

Synonyms :—Soamin, Sodium-p-arsanilate, Arsamin, Trypoxyl, Atoxylon.

It is a white odourless crystalline powder with a saline taste, soluble in 6 parts of water and 125 parts of alcohol. It contains 27.2 per cent. of arsenic. Under the misleading name of atoxyl (for the substance is quite toxic), it was extensively used at one time in trypanosomiasis (sleeping sickness), syphilis and other protozoal diseases. A number of compounds similar to atoxyl have been tried in trypanosomiasis. *Soamin* is practically identical with atoxyl, differing only in the amount of water of crystallisation. *Arsacetin* resembles atoxyl closely in its effects. Atoxyl on account of its property of getting decomposed in the gastro-intestinal tract is not given by the mouth but is usually given hypodermically or by intramuscular injections into the buttock in 10 per cent. solution. The dose is 0.02 to 0.2 gm. every other day. It is non-irritant, is absorbed rapidly and circulates in the blood longer than the arsenites and can therefore exert its parasitocidal action for a much longer time than the latter group of drugs. Atoxyl deteriorates by storage ; its solutions should therefore always be freshly prepared and sterilised before use.

Atoxyl has no action on the trypanosomes *in vitro* and can only become effective when it undergoes certain changes in the body. Most of it passes through the body unchanged and the small portion which remains is changed into bodies which are capable of destroying the parasites. The active therapeutic agent is probably arsenic and the reason why atoxyl is superior to inorganic preparations is that owing to its solubility it can penetrate into the tissues more rapidly than the inorganic preparations. There has been some discussion as to how its specific action is produced in the body. Some believe that part of the atoxyl is split up in the tissues, giving rise to an inorganic arsenic which is the active agent, and there is no doubt that inorganic arsenic destroys the parasite both in the blood and *in vitro*. This arsenic may

be liberated in the bodies of the parasites into which atoxyl has penetrated. Ehrlich held that it is partially reduced in the tissues and that the product of reduction is an active trypanocidal body. This was the idea which led him to seek for active trypanocidal drugs in the reduction products of atoxyl. Experimentally, the reduction was effected by chemical agents like hydrochloric acid, sulphurous acid, etc., and the resultant products were tested for their trypanocidal properties *in vitro*. A long series of experiments on this line eventually led to the preparations of salvarsan and neosalvarsan. One of the reduction products of atoxyl is *p*-hydroxyphenyl arsenious acid which kills trypanosomes *in vitro* in high dilutions, while atoxyl has no toxic effect in 5 per cent. solutions. The enormous changes in toxicity produced by reduction are thus obvious.

Effects on animal trypanosomiasis. Thomas and Breinl (1905) found that atoxyl cures experimental trypanosomiasis in mice; Koch (1907) reported beneficial results in similar infections. Favourable results were also obtained in chicken spirillosis. Voegtlin and Smith (1920) showed that the maximum tolerated dose (M.T.D.) of anhydrous atoxyl is 239 mgm., the minimum lethal dose (M.L.D.) 358 mgm. and the minimum effective dose (M.E.D.) in experimental trypanosomiasis is 89.6 mgm. per kilo. body weight.

Therapeutic uses. Atoxyl was introduced in the treatment of trypanosomiasis many years ago and in spite of the many new preparations that have been introduced it still continues to hold its field. Unfortunately it does not eradicate the disease in all its stages. It acts efficiently on the parasites in the blood, but has less effect on those which have infected the lymph glands, and apparently it does not reach those present in the central nervous system in sufficient concentration to destroy them. On administration of this drug the parasites disappear from the blood, but the supply is being constantly renewed from foci in the lymphatic glands and in the nervous system. Although cases of complete cure are on record, in the majority of cases it only alleviates symptoms and may prolong life. Small doses, such as 0.5 to 0.75 gm. weekly in an adult gave poor results and failed to avert relapses; 0.015 to 0.02 gm. per kilo, or 1 to 1.25 gm. gave good results. Of 84 cases in the first stage of the disease treated in this way, only five relapsed in seven to sixteen months. In the second stage, moderate doses decreased the meningeal reaction, as shown by the degree of lymphocytosis and clinical amelioration, but the effects were

of short duration. Chesterman (1925) recommends 1 gm. doses weekly for ten to twelve weeks.

Atoxyl was also used in the treatment of syphilis but the frequency with which it causes optic atrophy and blindness precludes its use for prolonged treatment of any disease. Soamin has been used in the treatment of many obscure conditions by medical practitioners in India. Intramuscular injections of this drug are given in asthma, anæmia and debility, affections of the respiratory and gastro-intestinal tract, filariasis, chyluria, apparently with good results. The drug probably acts as a hæmopoietic and as a tonic, but it appears to have no specific action in these conditions. It is given in increasing doses up to 5 grains twice a week and sometimes 20 injections or more may be given. It should be remembered however that soamin is a toxic drug and should be used with caution.

Toxic effects. Those produced with doses exceeding 0.5 gm. resemble the acute symptoms occurring in ordinary arsenic poisoning; these are dryness of the throat, headache, fever, colic, vomiting and diarrhœa, nephritis and paralysis of the lower limbs. The most serious effects are disturbances of vision, and these as a rule only occur when large doses of the drug are given at short intervals. They begin with scintillation, cloudiness, dimness and contraction of the field of vision, especially on the nasal side, which may lead to total and permanent blindness. Loss of vision can be easily produced in animals and is due to degeneration of the ganglion cells of the retina and later, of the fibres of the optic nerve. Though the retina is particularly susceptible, the cerebral cells are not immune and are also injured. Ophthalmoscopic examination shows at first no changes save that the retinal arteries may be narrowed and the veins somewhat hyperæmic; later there is complete optic atrophy. Evidence has been produced to show that the most important factor in the production of optic lesions is the presence of the amino group in the para position to the arsenic.

TRYPARSAMIDE

Synonyms :—Moranyl, Sodium-n-phenyl-glycinamide-p-
arsonate.

This compound is a derivative of atoxyl which was synthesized and developed in the Rockefeller Institute. Tryponarsyl Meurice is a Belgian product having a similar chemical composition. Like atoxyl it is a pentavalent compound. It is a white, odourless, crystalline powder containing 24.6 per cent. of arsenic. It is very soluble in water forming a neutral solution which is comparatively stable, so that a 10 per cent. solution can be boiled without decomposition. Its toxicity is very low and it is only slightly irritant and can be given intramuscularly, intraperitoneally (in animals) and intravenously.

The M. L. D. for monkeys is 1.25 to 1.5 gm. intravenously; slightly larger doses are required by the intramuscular route. Symptoms of intoxication are nervous and nutritional disturbances such as occur with all pentavalent compounds. There are tremors, inco-ordination of movements, clonic spasms, weakness and prostration; the appetite is lost and animals are emaciated and occasionally suffer from diarrhoea. The pathological changes consist of vascular dilatation, congestion, scattered petechial hæmorrhages and degenerative changes in internal organs. The minimum therapeutic dose for mice infected with *T. brucei* was found to be 0.2 gm. per kilo. when given subcutaneously and intravenously, and 0.275 gm. when given intraperitoneally within 24 hours after infection. The chemotherapeutic index for mice was 1:8 while for rats infected with *T. evansi* it was 1:3. Rabbits, rats and mice infected with *T. gambiense* can be more readily treated than those with *T. rhodesiense*.

Table showing M. L. D. of tryparsamide in animals in gm. per kilo. of body weight (Findlay, 1930).

Animal		Methods of Administration		
		Subcutaneous	Intravenous	Intraperitoneal
Mouse	...	2.75	2.0	2.0 to 2.25
Rat	...	1.0	.	0.75
Rabbit	...	1.10	0.75 to 0.90	1.10
Guinea-pig	...	1.50	...	1.50

Its trypanocidal activity *in vitro* is feeble as the organisms remain motile in 1 in 100 solution. In mice injected with *T. brucei* the trypanosomes rapidly disappear, the ratio between curative and lethal dose being 1 to 10 as compared with 1 to 4 of atoxyl. Amphoteric arsenical compounds, *i.e.*, those containing both basic and acidic groups, are said to be more frequently trypanocidal than the non-amphoteric.

Dosage and method of administration. In adults the dose is 2 to 3 gm. and in children 0.5 to 1 gm. according to age. The drug has been tried in sleeping sickness in doses of 2 gm. intravenously (0.112 gm. per kilo. body weight). Solutions should be freshly prepared, 2 to 3 gm. being dissolved in 10 c.cm. of cold sterile water. Such solutions should be clear but it is advisable to filter them through sterile filter papers, any turbidity necessitating the rejection of the solution. Boiling should be avoided as it may produce decomposition and toxic compounds. The drug is well tolerated intramuscularly in 20 per cent. solution; 30 per cent. solutions produce more discomfort and may lead to abscess formation. It may be given by this route but usually the intravenous route is preferred. Subcutaneous injections are not recommended as they produce irritation and supuration. Ten weekly injections of 40 mgm. per kilo. body weight in a 10 per cent. solution are considered safe. The toxic effects of this drug are confined to doses close to the M. L. D. and the recovery of animals from sublethal intoxications is remarkably rapid and complete. This makes possible the repeated administration of very large doses of the drug at comparatively short intervals without incurring the danger of cumulative toxic action. By taking advantage of this peculiarity of action, it is possible to develop such a high degree of tolerance on the part of the animals that doses larger than the M. L. D. can be given. This is a very important feature of the toxicological action of tryparsamide which is of great significance in the use of the drug for therapeutic purposes.

Toxic effects. Untoward effects with this drug are not commonly met with. The most serious such as amblyopia, nitritoid reactions and exfoliative dermatitis have not been noticed and jaundice is a rare complication. As a rule 80 to

90 per cent. of the drug is excreted during the first 24 hours after injection, but in certain individuals it is excreted slowly and they are more susceptible to the cumulative effects of the drug.

The untoward effects generally appear after the fifth or sixth injection, the symptoms consisting of a sensation of dazzling; on examination the fundus is found to be hyperæmic; the visual fields are contracted on the nasal side. In severe cases contraction goes on till complete blindness results. Involvement of the optic nerve is by no means rare in neurosyphilis. All such cases should therefore be thoroughly examined by an ophthalmologist before treatment with tryparsamide. In optic involvement, the result of injection should be carefully watched. Occasionally vomiting, slowing of the pulse and loss of consciousness may occur immediately after an injection, similar to those seen with arsenobenzene. Remote effects are shedding of the nails, albuminuria and dermatitis. Visual disturbances are seen with larger doses. If these occur, a suitable interval between injections prevents them. Doses of 3.0 gm. and over should not be given oftener than once a week. If amblyopia develops during the treatment of trypanosomiasis tartar emetic is substituted for 3 weeks. Sodium thiosulphate injections appear to be ineffective in preventing amblyopia.

Therapeutic uses. *Syphilis.* Experiments on rabbits showed that this drug possesses the power of tissue penetrability to a marked degree; extensive cutaneous and subcutaneous lesions in these animals retrogressed and healed very quickly under its effect. Tryparsamide is not effective against primary and secondary syphilis, nor against the gummata or earlier cerebro-spinal manifestations. It appears to possess the power of penetrating into the tissues, especially nervous tissues, to a much greater extent than some of the other arsenicals. It has been tried in neuro-syphilis with good results. Marked serological improvement is observed in the majority of cases of all types of syphilis but 50 or more injections are necessary, extending over a period of one year. Some cases of early paresis improve. Some authorities combine tryparsamide with weekly injections of 1 grain of mercury salicylate. There is general

agreement that in early cases of general paresis and tabes, treatment with tryparsamide is of considerable value, better results being obtained than with arsphenamine. The results, when the parenchyma is involved, are superior to those when the blood vessels and the meninges are affected, but while clinical improvement is soon manifested it requires about 80 injections of tryparsamide to render the serum reaction negative. The value of the drug is said to be due not to spirochæticidal action but to a general tonic action on the tissues. In neurosyphilis it is advisable to give courses of 8 to 15 injections of 2 to 3 gm. (not exceeding 0.04 to 0.05 gm. per kilo.) at intervals of not less than a week, with intermission of 2 months between the courses. Treatment is to be continued for several years. According to some, tryparsamide can be given safely where optic atrophy is present provided the patient is carefully watched. In cases of paresis and mania it is worthy of trial.

Trypanosomiasis. Tryparsamide is a very efficient trypanocide. Chesterman (1923) treated 40 cases in the Belgian Congo by 8 to 10 weekly intravenous injections of 3 gm. each dissolved in 10 c.cm. of water, with good results. The dose should not exceed 4 gm. and intrathecal administration is not recommended. Adults receiving less than 0.05 gm. per kilo. body weight generally relapse; children can stand comparatively much bigger doses and in these cases 0.1 gm. per kilo. can be given.

Marshall and Vassallo (1926) consider that tryparsamide gives comparatively much better results than Bayer 205 in the treatment of trypanosomiasis. Tryparsamide clears the blood in from 6 to 12 hours in doses of 1.5 gm. intravenously, in early infections due to *T. gambiense*; the peripheral blood remains free for such long periods as to suggest permanent cure. The drug is not effective in infections with *T. rhodesiense*.

Weekly injections of 2 to 3 gm. in adults have been recommended because such doses give equally good results as large and more frequent doses, and because they reduce the chances of ocular disturbance to the minimum. In the first stage of the disease a total dosage of 20 to 50 gm. suffices to produce a

cure. The blood and glands become permanently negative, there is marked clinical improvement in those cases in which the spinal fluid is only slightly changed before treatment, and it tends to become normal with the treatment. In the second stage it is necessary to give 50 to 100 gm. The patients who exhibit nervous and mental symptoms are said to show rapid and considerable improvement; in cases of moderate intensity the benefit obtained is marked and constant. The action is said to be rapid, durable, constant and is definitely superior to any other known drug. Relapses or incomplete cures are always due to extraneous causes such as insufficient dosage, irregularity of the injections and difficulties due to the patient. Toxic reactions, acute or chronic are negligible. Blindness which occurs after treatment with tryparsamide is in most cases due to previous arsenical treatment. The drug not only has curative effects but probably has prophylactic properties as well.

Tryparsamide is said to have a beneficial effect on general nutrition in addition to its parasitotropic effects, and some clinicians believe that its chief action is to build up the resistance of the body to combat infection.

Prophylactic use. Tryparsamide has not been extensively used as a prophylactic drug in sleeping sickness in man. In vaginal infections in animals (rabbits) it has a well marked prophylactic effect. This may be worth testing. Further experience of its use on a large scale is required to ascertain how far the systematic use of the drug in all the infected persons in any area will enable new infections to be reduced.

STOVARSOL

Synonyms:—Ehrlich 594, Fournau 190, Acetarstone, Kharophen, Orarsan, Osvarsan, Stovarsolan, Acetylamino-oxyphenyl-arsonic acid, Spirocid, Troposan. It contains 27.2 per cent. of arsenic.

Pharmacological action. It is absorbed rapidly, has a low toxicity and is excreted rapidly in the urine. Saullet (1927) found that stovarsol was lethal to *E. histolytica* culture within 24 hours, in dilutions of 1 in

600. He noted that it was more active in the presence of liver extracts. It is a safe drug, is easy to administer, has a marked effect on the hæmopoietic system and acts as a good general tonic.

Therapeutic uses. *Syphilis.* It was first introduced into medical practice in 1921-22 in the treatment of malaria and amœbic dysentery, as a prophylactic against syphilis, and for the treatment of spirochætal infections. Administration by the mouth produced healing of primary lesions in rabbits and monkeys. In syphilis in man 1.0 gm. of stovarsol by the mouth for one week, followed by another course at the interval of a week till 12 to 16 gm. were given, healed the primary chancre. Secondary and tertiary lesions are said to have also disappeared. It is useful in the treatment of general paralysis, especially when there are megalomania or psychical disturbances. The serological reactions improve in one-third of the cases. Congenital syphilis of infants has been treated with stovarsol; the doses recommended are 0.12 gm. daily for 4 days to a total of 6.6 gm.

Yaws. 0.5 to 1.0 gm. daily given by the mouth before food on alternate days for 15 to 17 days generally clears up the lesions. Sodium stovarsol 0.5, 1.0 and 1.5 gm. may be given intravenously at intervals of 48 hours to a total of 9.0 gm.

Amœbic dysentery. Marchoux (1923) appears to have been the first to test this drug in the treatment of amœbiasis. The drug was used in those cases who had resisted emetine treatment, in doses of 0.25 gm. in pill form twice daily for a period of 10 days. Amœbæ or cysts were found in the stool even after the treatment. Petzetakis (1925) tried the drug extensively and found it an excellent remedy for parasitic infections of the intestinal tract; in infants the doses recommended up to one year of age are 0.05 to 0.08 gm. daily; from 1 to 2 years, 0.08 to 0.10 gm.; from 2 to 5 years 0.10 to 0.25 gm. daily. In chronic and relapsing cases of amœbiasis prolonged treatment is necessary and may be supplemented by injections of emetine. He found that the drug can be exhibited over prolonged period without producing any ill effects. To avoid toxic symptoms, which frequently occur with the drug, the dose should not

exceed two tablets (8 gr.) daily for 10 days or 1 tablet (4 gr.) daily for 20 days. Brown (1926) considers that stovarsol is more effective in eradicating amoebæ than emetine. Van Steenis (1927) found stovarsol less effective than emetine or yatren, but very useful against the 'minuta' type of *E. histolytica*.

Knowles (1928) in summing up the literature on stovarsol, says that it is apparent from the large series of papers that on the whole the results are not too bad. Almost every writer comments on the drug as one easy to administer and well-tolerated by the patient. On the other hand it has less powerful amoebicidal action than emetine, and some authors comment on its toxic effects. Occurrence of a measles-like rash was not uncommonly met with and cases of acute exfoliative dermatitis have been recorded after administration of stovarsol. Knowles treated 32 patients, mostly chronic, in Calcutta; the ratio of probable cures to failures in these was 1:1.1. He is of opinion that stovarsol has a definite place in the treatment of chronic intestinal amoebiasis. The ease and simplicity of the treatment are remarkable. The usual course is one tablet of 4 grains each night and morning for ten days. No toxic symptoms were observed, while the drug undoubtedly has a hæmatinic value; the patients taking stovarsol are not miserable and unhappy beings like those on emetine or emetine-bismuth-iodide treatment. The average cost of treatment is 2 to 3 rupees. It is particularly useful in chronic cases and the chance of eradication of the infection is 40 to 50 per cent. The drug was used by Knowles as an after-treatment, the relief of clinical symptoms being first obtained with emetine injections and bismuth treatment. The patient was then given a few days' rest and a ten-day course of stovarsol afterwards. This usually leads to rapid improvement in general health and the infection may be eradicated. For chronic carriers stovarsol may be followed by a course of emetine-bismuth-iodide.

Malaria. Stovarsol was first used in the treatment of malaria in 1923 and it was reported to be effective against tertian and quartan infections. Intravenous injections of 1.0 gm. of sodium stovarsol in 10 c.cm. of distilled water were found to

be effective in patients artificially and naturally infected with *P. vivax*, the parasites disappearing from the blood. The drug appeared to have an action especially on the older pigmented parasites, older schizonts and gametocytes in contradistinction to quinine, which attacks the younger forms. While stovarsol in 1.0 gm. doses produces disappearance of *P. vivax* from the blood, *P. falciparum* and *P. malariae* are not touched according to many observers. The action of stovarsol on various stages of *P. vivax* has been studied. It would appear that the parasites are only destroyed when they reach a certain developmental stage, while the younger forms are not touched. Sinton found the relapse rate in benign tertian malaria treated with stovarsol smaller than with the cinchona alkaloids. Severe rigors sometimes follow within 18 hours of injection of stovarsol in malaria, resembling those occurring with neosarsphenamine. It is possible those are due to liberation of toxin after rapid destruction of the parasites.

Quinine stovarsol is a compound of quinine with stovarsol. It causes disappearance of the crescents in from 3 to 36 days, but the schizonts are not so readily affected.

Relapsing fever. Stovarsol in doses of 1.5 gm. by the mouth is said to cure relapsing fever, the spirochaetes disappearing in 6 to 30 hours. Others have had disappointing results. It has also been used for prophylactic purposes.

Stovarsol has also been employed in the treatment of intestinal parasites such as lambliasis. Stovarsol orally and by injections has been tried against trypanosomiasis by many workers but without success.

Calcium stovarsol phosphate known as *Realphene* has been tried in syphilis with good results. It is a good general tonic.

Toxic symptoms. Cases of poisoning with stovarsol, following its administration in dysentery in 2 gm. doses daily, have been recorded. Fever was the first symptom followed 2 days later by diffuse erythema, dryness, pruritus and urticaria. Rashes appeared all over the body and on the legs and face; in severe cases it may pass on to exfoliative dermatitis. Oedema, jaundice, colic, diarrhoea, albuminuria, coryza, bronchitis, urticaria, ocular troubles, giddiness, collapse and glycosuria may occur. Acute nephritis with casts in the urine may occur after injection. The drug should not be given for more than 10 days at a time, the second course should be given after a suitable interval. In Sinton's series no toxic symptoms occurred, probably because he used

magnesium sulphate which eliminated arsenic from the gut, or possibly because the liver and kidneys were protected with glucose and alkali.

TREPARSOL

Synonyms:—Fournau 257, Sodium-3-formylamino-4-oxyphenyl-1-arsionate, Formyphenarsine.

It is said to be suitable for administration by the mouth in 1.0 gm. doses in the treatment of malaria, syphilis, yaws, etc. Good results were reported to have been obtained in dengue when the drug was given by the mouth in doses of 0.75 to 1.5 gm. on four consecutive days. In the intestines treparsol is split up into formic acid and meta-amino-para-oxyphenyl arsenic acid which is the active principle of stovarsol and is said to act directly on intestinal parasites, specially protozoa. In combination with emetine it is said to have some effect in infections due to giardia and trichomonas, it has not been used against amoebic dysentery. Although courses extending over 4 weeks have been recommended it is not advisable to give it for more than 10 days at a time. Slight diarrhoea may occur and fatal cases have been recorded after prolonged use. Treparsol is excreted mostly in the urine.

Fournau 270 (sodium-4-acetylamino-2-hydroxyphenylarsinate). It is a white powder readily soluble in water and can be injected subcutaneously; it is painless, produces no local reactions and is rapidly absorbed. The drug has been tried in human trypanosomiasis but is not so effective as tryparsamide. It has been tried for prophylactic purposes in animals but is less efficient than tryparsamide.

Fournau 269 & 417. (4-amino-2-hydroxyphenylarsinic acid and 4-formylamino-2-hydroxyphenylarsinic acid). Both these drugs can be given by the oral route. Fournau 417 has a chemotherapeutic index of 1 : 16 when given by the mouth and 1 : 5 when given subcutaneously. These drugs are at present under trial.

Acetylarsan (hydroxy-acetyl-aminophenylarsinate of diethyl amine) can be given by intramuscular and subcutaneous injections, but headache, vomiting and diarrhoea are frequently produced; erythema, albuminuria, and jaundice may occur. In trypanosomiasis 12 gm. are given in 16 injections of 0.75 gm. each at intervals of one week; the results are inferior to tryparsamide. The primary and secondary lesions of syphilis are said to be favourably influenced. One to 3 injections of 12 to 50 mgm. per kilo. produce rapid results in primary, secondary and tertiary yaws. In relapsing fever it is considered more effective than arspenamine.

B. R. 68. This drug, prepared by Binz and Rath (1927) differs from others in that the arsenic is not linked to a benzene nucleus. The drug produces febrile reactions and vomiting and is useless in infections due to *T. rhodesiense*.

B. R. 34 is said to be effective in doses of 0.2 gm. intravenously freeing the blood of trypanosomes.

B. R. 34A. is a pyridine preparation of arsenic and is effective against *T. brucei* infections in mice. Its chemotherapeutic index is 1: 20.

Hoechst 2754. This compound is said to be closely related to tryparsamide and can be given intravenously in 2 gm. doses. It is said to have a definite action in the second stage of trypanosomiasis but is apt to produce nephritis.

Trivalent Compounds of Arsenic

SALVARSAN

Synonyms:—Kharsivan, Dioxy-diamino-arseno-benzol dihydrochloride, Arsenobenzene, Arsenobenzol, Arsphenamine, Arsenobillon, Arsen-phenolamine, Amino-arsenophenol, Ehrlich-Hata 606.

Salvarsan was first prepared by Bertheim and tested by Ehrlich and Hata in 1910. The dose for women is 0.3 to 0.4 gm. and for men 0.4 gm. in 200 c.cm. of solution medium. It is prepared from atoxyl by reduction and combination of two of its molecules to form a trivalent dihydroxyl-diamino-arsenobenzene which is a stable preparation. It is a yellow crystalline powder containing 31.5 per cent. of arsenic; it is readily oxidised in the air and so is kept in vacuum tubes. Salvarsan though it does not kill spirochaetes *in vitro* has a very pronounced effect on these organisms *in vivo*. It is fifty times less toxic for experimental animals than mercury. The M.L.D. for mice is 143 mgm. per kilo. and for rabbits 100 mgm., when given intravenously. In rats showing a trypanosome count of 150,000 to 250,000 per c.cm. of blood, temporary sterilisation could be effected with doses of 6 mgm. and permanent sterilisation with doses of 8 to 12 mgm. per kilo. Mice infected with the spirochaetes of relapsing fever were sterilised with 10.6 mgm. per kilo. and rabbits inoculated with syphilis were cured with 23.5 mgm. per kilo. given intravenously.

Salvarsan has the disadvantage of having an acid reaction in solution and therefore has to be neutralised at the time of

use. For this reason it has been mostly replaced by neo-salvarsan. A solution which is not fully neutralised or one which is over-alkalinised is depressant for the heart. In feeble patients or when the central nervous system or the heart is affected smaller doses should be given. Generally a course of 4 to 8 doses is recommended, the injections being given at intervals of 8 to 10 days, often in conjunction with mercury.

Neutralisation is best effected by adding to the salvarsan solution 15 per cent. caustic soda solution to precipitate the base (0.28 c.cm. for 0.3 gm of the drug) ; dilute with a little 0.5 per cent. saline and then add just enough caustic soda solution to dissolve (about 0.6 c.cm. in all) ; finally dilute to 300 c.cm. with 0.5 per cent. saline solution.

NEO-SALVARSAN

Synonyms :—Neo-kharsivan, Ehrlich 914, Novarsenobenzol, Novarsan, Novarsenobillon, Metarsenobenzol, Neo-arsenophenolamine, Sodium dioxy-diamino-arsenobenzene-methanesulphonate.

This is a condensation product of salvarsan. It differs from salvarsan in that it is not a combination of dioxy-diamino-arsenol-benzol with HCl but with sodium methane sulphonate. It is a yellow powder, readily soluble in water, giving a neutral solution. It is a stable preparation and readily dissolves in water forming a neutral solution, it can therefore be injected intravenously in concentrated form. The dry powder must contain not less than 18 per cent. or more than 21 per cent. of arsenic; according to U.S.P.X. it should not contain less than 19 per cent. of arsenic.

The experiments for testing the action of neo-salvarsan were chiefly conducted on the spirochaetes of relapsing fever in rats and mice, and subsequently in fowls and also on the treponema of syphilis. It was found that a single non-toxic dose freed the animals completely from spirochaetosis and protozoa. *In vitro* experiments show that during the first 10 hours even

1 in 100 concentrations have no effect on the spirochætes, but after 15 hours there is marked reduction in their number and eventually all are destroyed. The maximum dilution for killing them was 1 in 200,000 as compared with 1 in 2,500 for *Bact. coli*.

When injected intravenously into rats, neo-salvarsan is about two and a half times less toxic than salvarsan. The maximum tolerated dose of the American product in rats is 254 mgm. per kilo. body weight, in mice it is 250 mgm. and in rabbits it is 200 mgm. when given intravenously. The average minimum curative dose of neo-salvarsan for rats infected with *T. equiperdum* is 4 to 6 mgm. intramuscularly and for rabbits inoculated with syphilis 30 to 40 mgm. intravenously. The hydrogen-ion concentration of neo-salvarsan is 7 to 7.4 which is the same as that of the blood, while that of a properly alkalised solution of salvarsan is more than 9. It therefore causes less biochemical disturbances in the blood and tissues. Although some syphilologists still regard salvarsan as being superior to neo-salvarsan, the latter is nevertheless more widely employed and exerts practically the same favourable influence upon the disease and certainly possesses a greater factor of safety.

Dosage. This should be regulated according to the general condition of the patient. In the male adult the starting dose of salvarsan is usually 0.2 gm. which is increased by 0.1 gm. at every successive injection till a maximum of 0.6 gm. is attained. For females, the starting dose is 0.2 gm. and a maximum of 0.4 gm., for children 0.1 to 0.3 gm.; for infants 0.02 to 0.1 gm. The dose of neo-salvarsan is about $1\frac{1}{2}$ times that of salvarsan. The ordinary course is 6 to 8 intravenous injections given at intervals of 7 to 10 days. With very early cases, the first 2 or 3 injections may be given 3 or 4 days apart. The patient is allowed 6 to 8 weeks' rest and then another course is given and this in early cases may be repeated till 3 or possibly 4 courses have been given. Mercury is also given with the courses and semi-annual courses of mercury may be kept up for 3 years

Co-ordination Compounds

• The chemotherapeutic effect of co-ordination compounds of salvarsan and neo-salvarsan equals that of salvarsan and neo-salvarsan.

Silver salvarsan or **silverarsphenamine** is a metal arsenobenzene compound. It is a brownish-black powder, readily soluble in water, giving an alkaline solution. It contains 22.5 per cent. of arsenic and 14 per cent. of silver, probably in the form of silver oxide. It is given intravenously in doses of 0.1 to 0.2 gm. for women and 0.25 gm. for men at weekly intervals. In feeble patients begin with 0.05 gm. or 0.075 gm. Generally 0.1 gm. is dissolved in 10 c.cm. of sterile water making a 1 per cent. solution. Clinically 0.1 gm. of this drug corresponds to 0.3 gm. neo-salvarsan. Sodium silver salvarsan is another preparation in which the silver is not combined with salvarsan but exists in a colloidal state.

Neo-silverarsphenamine or **neo-silver salvarsan** is a molecular compound of neo-salvarsan and silver and is a brown powder. Sodium silver neo-salvarsan is yet another preparation. Neo-silver salvarsan is said to be about half as toxic as silver salvarsan and slightly more toxic than neo-salvarsan; its maximum tolerated dose is 278 mgm. per kilo. of mice as compared with 167 mgm. of silver salvarsan and 370 mgm. of neo-salvarsan. These compounds have been used in the treatment of syphilis and produce remarkable results on visible syphilitic lesions. With these compounds the characteristic and often nauseating garlic-like odour is absent. They have not been known to produce argyria. It was thought that silver compounds of salvarsan were probably twice as effective as neo-salvarsan in similar doses, but this has not been proved. In multiple sclerosis silver salvarsan, in doses of 0.05 gm. increased to 0.2 gm. twice weekly, is said to be an effective remedy.

The silver compounds should be given with caution in cardiac disease and diseases of the liver and kidney and when there is a tendency to skin disease.

Sulpharsphenamine. Synonyms:—Sulfarsenol, Sulpharsenobenzene, Kharsulphan, Myosalvarsan.

This was originally a French preparation. It is a fine yellowish powder which dissolves easily in water giving a neutral solution which can be given intravenously, subcutaneously or intramuscularly. It contains 20.7 to 23.6 per cent. of arsenic and 8.7 to 12.8 per cent. of sulphur. Chemically it is dioxy-diaminoarsenobenzene-dimethylene sulphonate. Dose 0.12 to 0.18 gm. for the first injection in 2 to 3 c.cm. of distilled water, gradually increased to 0.45 to 0.6 gm. For intravenous injections 0.06

gm. is the starting dose but Harrison (1921) does not recommend the intravenous use of the drug as dermatitis and other untoward effects are more likely to follow by this route. The M.L.D. (minimum lethal dose) of this drug in white rats ranges from 320 to 480 mgm. and the M.E.D. (minimum effective dose) from 15.9 to 31.5 mgm. per kilo. when given intravenously. When given intramuscularly or subcutaneously, the M.L.D. is 400 to 700 mgm. and the M.E.D. is 15.6 to 34 mgm. per kilo. body weight. It is the only arseno-benzol compound on the market which appears to be equal in efficiency to salvarsan or neo-salvarsan in the treatment of syphilis when given by the hypodermic or intramuscular route; it is therefore useful in children and for obese persons with veins difficult to find; such strong solutions as 20 to 30 per cent. can be given without untoward symptoms. The drug is useful in patients who develop shock or nitritoid reactions. It is therapeutically just as effective and is specially well borne by children with congenital syphilis. Dermatitis and jaundice may be produced by it, but acute symptoms such as nausea, vomiting and diarrhoea are less common; the incidence of general reactions is also lower.

Harrison (1923) recommends it when myocarditis and aneurism are present. It is specially indicated in the treatment of congenital syphilis, in gonorrhoeal arthritis and puerperal septicæmia. The following table from Martindale gives the dosage for a course in primary syphilis for an average adult.

Day	Dose	Quantity of sterile water
1	0.12 to 0.18 gm.	2 to 3 c.cm.
3	0.18 to 0.3 gm.	3 to 5 c.cm.
5	0.30 to 0.42 gm.	5 to 7 c.cm.
8	0.42 to 0.6 gm.	7 to 10 c.cm.
13	0.48 to 0.6 gm.	8 to 10 c.cm.
19	0.54 to 0.6 gm.	8 to 10 c.cm.
25	0.6 gm.	8 to 10 c.cm.

After the 40th day, do a Wassermann test and a second course to be started on the 61st day in sero-negative primary

cases; in sero-positive primary cases 3 or more courses may be necessary.

Thiosarmin or disodium-dioxy-diamino-arsenobenzene-methylene sulphonate has been prepared in the Brahmachari Research Institute, Calcutta. It is very closely allied to other sulpharsenobenzene compounds such as sulfarsenol, kharsulphan, sulpharsphenamine, etc.

Thiosarmin is a light yellow powder readily soluble in water, almost neutral in reaction and having a hydrogen-ion-concentration of 7.2 to 7.4. It is fairly stable and does not change its colour, even on standing for 48 to 72 hours. When heated it decomposes without melting. The arsenic content varies from 19.5 to 25 per cent.

Toxicity. The toxicity of the compound is very low and compares favourably with similar preparations. Denham-White and Brahmachari (1933) found that the toxicity of thiosarmin, sulfarsenol and sulpharsphenamine is almost the same in experimental animals. Given intravenously in white rats the maximum tolerated dose of thiosarmin was 300 mgm. and the minimum lethal dose 490 mgm. per kilo. of body weight. The minimum lethal dose in the author's series of experiments, when given intravenously in a 2 per cent. solution in white mice, was found to be between 425 to 450 mgm. per kilo. of body weight.

Thiosarmin is indicated in all stages of syphilis. Local lesions are said to heal up after a few injections and the results of the Wassermann reaction are very encouraging. The dosage recommended in syphilis is to begin with 0.15 gm., increased by 0.15 gm. in subsequent injections to a maximum single dose of 0.6 gm. Below 16 years $\frac{2}{3}$ full dose is given and children below that age should receive proportionate dosage. The drug should be dissolved in redistilled water, boiled and cooled. A 10 per cent. solution is slowly injected intramuscularly in the gluteal region. It can also be given subcutaneously or by the intravenous route.

Amongst the advantages claimed for the drug are absence of reaction, the temperature does not rise, and the danger of nitritoid crises or anaphylactoid conditions is negligible. In

some cases, however, signs of intolerance follow injections of thiosarmin which call for immediate suspension of the treatment. Cardiac degeneration, nephritis, severe diabetes, cirrhosis of liver are contraindications to its use.

Bismarsen or bismuth arsphenamine sulphonate. It is one of the co-ordination compounds of arsphenamine, the bismuth being linked to the arseno group in the same way as silver, gold, etc., to their respective compounds. Chemically it is trisodium-3-amino-4-hydroxyphenylarseno-n-methylene-sulphonate dibismuth, having the empiric formula $C_{21}H_{21}O_{12}As_2Na_3S_2N_3Bi_2$. Bismarsen is a brownish-yellow amorphous powder freely soluble in cold water. The arsenic content of the preparation ranges from 12 to 15 per cent. while bismuth occurs in proportion of 23 to 25 per cent. One great advantage of the drug is that it can be given intramuscularly, thus avoiding many of the technical difficulties of intravenous arsenic medication, and at the same time the combination of bismuth and arsphenamine enhances the spirochæticidal activity to an extent greater than the summation of these two drugs separately. Kolmer (1930) found that in rats infected with *T. equiperdum*, the minimum curative dose by the intravenous route was 0.012 gm. per kilo. and by intramuscular injection, 0.015 gm. per kilo. body weight. In experimental investigation in rabbits infected with syphilis, the minimum single curative dose was approximately 0.015 gm. per kilo. by intravenous route and from 0.015 to 0.030 gm. per kilo. by intramuscular injection. Stokes and others (1931), in their appraisal of this new synthetic compound, concluded that it is a safe, relatively non-toxic and efficacious drug for administration in syphilis. They consider it a valuable substitute for arsphenamin in reactive patients, though slower in action. Herxheimer's reaction and nitritoid crisis are very rare; the effect on the Wassermann reaction is very encouraging and the proportion of all forms of relapse in a series of early syphilitic cases was 12 per cent. as compared with from 20 to 40 per cent. in cases treated with other drugs.

The method of administration in syphilis is to give it intramuscularly in 0.2 gm. doses, dissolved in 1 c.cm. of

distilled water, to which 2 minims of 2 per cent. solution of butyn are added to minimise the local painful reaction. Generally 4 or 5 courses are given, each course comprising about 8 injections, twice weekly, and the interval between each course being one month. The occurrence of dermatitis or jaundice during the treatment necessitates the stoppage of all injections. Special value has been given to bismarsen in the treatment of cardiovascular syphilis for its tissue-soluble properties and for its effect on Wassermann fast syphilis.

Mode of action of organic arsenicals. Ehrlich's original idea was that these drugs had a simple parasitocidal action and that certain chemical chains in the drugs had a selective chemical affinity for certain side chains in the protoplasm of the organisms and therefore the organisms were killed without harm to the host; this idea has now been given up. That organic arsenical compounds are converted into trivalent oxides before parasitocidal action is brought about, has been experimentally shown. Several drugs have no action upon trypanosomes *in vitro*, but have a considerable trypanocidal action *in vivo* and it has been proved by experiments that these drugs are in many cases changed in the body from relatively inactive to more active forms. Hata working in Ehrlich's laboratory showed that arseno-benzene does not kill spirochaetes *in vitro*. In the Hygienic Laboratory, U.S.A. Public Health Department, it was shown that a partial oxidation of arsenobenzene occurs. The compounds of R.As.=O type (arsenious acid, arsenoxide) in dilutions of 1 in 10,000 render trypanosomes non-infectious *in vitro* and kill the trypanosomes in rat's blood immediately after injection. The compounds of R.As.=As.R. (salvarsan) type in similar doses have little action on trypanosomes for the first hour and do not kill 90 per cent. of the parasites after 2 or 3

hours; pentavalent compounds of R.As. $\begin{array}{c} \text{OH} \\ \diagup \\ \text{O} \\ \diagdown \\ \text{OH} \end{array}$ type are still less

effective. It seems that it is the persistent effect of minute quantities of the oxide, far below the concentration immediately lethal *in vitro*, maintained for sometime, which is responsible for cures. From this point of view the superior activity of *arseno-compounds*, which form a depot from which minute quantities of the oxide are continuously given off, can be understood. Dobell and Laidlaw (1926) have shown that persistence of action for long periods is a very important point in the amoebicidal action of emetine and probably the same is true of the arsenicals. In toxic doses the first class of compounds produce immediate toxic effects while the other two classes only produce toxic effects after considerable delay. Salvarsan incubated at 37°C. with animal tissues for 3 hours produced immediate effects upon rat trypanosomes and its toxic action

was intensified. Salvarsan is found to destroy cultures of spirochaetes in the test tube only in concentration of 1 in 1,000 but incubation and digestion by the tissues change salvarsan into bodies of the nature of arsenoxide by which both the spirochaeticidal and toxic action are intensified. In the body, trivalent compounds have very little immediate effect on trypanosomes. After 24 hours these compounds produce death in extremely low concentration—one part in several hundred millions.

A new conception of the arsphenamine treatment of syphilis is offered by Anwyl-Davis. While watching *S. pallidum* for days by the dark ground method he found that when bathed in salvarsanized serum they gradually lose their normal appearance, become ghost-like, fragmented and paralysed and in about five days apparently die. About 5 or 6 hours later they recover their normal appearance, are revived, regain their spiral and motility and become as normal and as active as controls that have not been 'doped.' This strongly suggests that arsphenamine should be injected at intervals of five days or less instead of waiting for the customary week. The organisms should be attacked with fresh drug when their vitality is lowest so that they may not multiply or develop resistance.

These drugs are examples of compounds whose therapeutic efficiency is due to changes which take place in them in the body. Their therapeutic efficiency is estimated by determining the ratio between the sterilising dose and the tolerated dose though this is liable to error on account of the resistance of different species of trypanosomes and also of the animals. Voegtlin and his associates (1923) have advanced the theory that arsenic in the form of trivalent oxides ($\text{R.A.s.}=\text{O}$) is the active form and is a specific poison for the sulph-hydryl SH groups of compounds like glutathione and possibly other SH compounds present in the protoplasm of the parasites. The glutathione group is concerned in the oxidation and reduction processes in the living cells and Hopkins and Dixon (1921) showed that compounds containing an SH group, such as the reduced form of glutathione, sodium-thioglyco-collate, etc. counteract the toxic action of arsenoxide on these trypanosomes, both *in vitro* and in the circulating blood, presumably by an union of the arsenic with these compounds by means of their SH group, before the arsenic has united with the SH group of the parasites. The organotropic action is also reduced. Arsenic therefore in the form of an aromatic arsenious compound may be regarded as a specific poison which acts by combining with the SH compound in the protoplasm and its effects can be counteracted by introducing the SH compound artificially, to take the place of those present in the protoplasm. The organic compounds of arsenic are examples of drugs which are introduced into the body in a relatively inert form and are changed by the body tissues to therapeutically powerful compounds. The relative activity of different

organic arsenicals is given in table modified from Clark's Applied Pharmacology (1933).

Compound.	Percentage of arsenic	M.L.D. for rat*	M.C.D. in rat infected with <i>T. equiperdum</i> *	Ratio $\frac{\text{M.L.D.}}{\text{M.C.D.}}$
1. Arsenic acid ...	53	50	37.5	1
2. Atoxyl (arsanilic acid) ...	27.2	150	37.5	4
3. Arsenious acid ..	69	7	7	1
4. p-Hydroxy-m-amino-phenyl-arsen-oxide ...	31.8	10	0.75	13
5. Salvarsan. ...	34	75	2.0	37
6. Neo-salvarsan .	21	100	3.0	33

STANDARDISATION OF SALVARSAN AND ALLIED COMPOUNDS

Standards of toxicity of salvarsan and its allies. All trivalent organic arsenicals are highly reduced bodies. If reduction is carried out with insufficient vigour they become rapidly contaminated with a much more toxic oxidation product, arsenoxide (3-amino-4-hydroxy-phenyl-arsenic oxide). One of these compounds is 20 times more toxic than the pure hydrochloride of an arseno compound. It is impossible even by the most careful production, to exclude completely the more toxic oxides and commercial samples contain from 0.4 to 5 per cent. of arsenoxide. Oxidation may also occur during the process of preparation of solutions. It is the duty of the manufacturers to see that no batch of this product contains these in unsafe proportions. The extent of contamination can be chemically determined with some degree of accuracy. There are also indications that other toxic products of unknown constitution may arise through uncontrollable accidents in preparation. The Board of Trade has made a condition that all samples prepared should be subjected to biological tests by an approved authority. In addition, every sample is further tested by intravenous injection in rabbits in doses only slightly less than that which may be expected, according to Ehrlich's publication, to be lethal for the animals. In order to ensure that arsphenamine preparations are not toxic and are of definite therapeutic value, certain standardisation tests have been introduced. Every batch prepared has to be tested. Arsphenamine has now been discarded in favour of neoarsphenamine preparations, and tests have been evolved for this. The chemical composition of this product of manufacture has never corresponded closely with the theoretical formula. By slight modifications of manufacturing process, substances of low toxicity can be produced to pass the official

*Dose expressed in cubic centimetres of N/10 solution of arsenic per kilo. of bodyweight.

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tests. Lowering of toxicity however seriously weakens the therapeutic efficiency. Tests for therapeutic standardisation have therefore been introduced.

Rats and mice infected with trypanosomes are preferred to fowl spirochaetes of relapsing fever, since trypanosomiasis in the latter assumes an acute course resulting in death of the animal. *T. equiperdum* is preferred to other trypanosomes. The number of trypanosomes per c.mm. of blood of a seed rat is counted, an inoculum of definite strength is prepared and this is injected intraperitoneally. In 24 hours these rats will have a definite number of parasites per c.mm., those having 100,000 to 150,000 per c.mm. are preferred. The drug to be tested is then dissolved in distilled water and a known quantity of the drug is given intravenously. The minimum effective dose (M. F. D.) is the dose of the drug required to bring the trypanosome count to negative within 24 hours, i.e., the dose of the drug which kills 100,000 to 150,000 trypanosomes. Greater accuracy is obtained if the blood is not only examined 24 and 72 hours after injection, but also 21 days later. The question of drug resistance has to be borne in mind.

Dale, White, Burn and others in England use mice instead of rats. The strain of *T. equiperdum* is propagated in rats, and mice are infected by an intraperitoneal injection of 0.1 c.cm. of an emulsion of rat's blood in 1.0 per cent. sodium citrate solution, so that 7 to 8 million of trypanosomes are injected. Ten days later the mice showing 100,000 to 500,000 trypanosomes per c.mm. are selected. The smallest dose which causes a complete disappearance of trypanosomes within 72 hours is termed the minimal curative dose. Dale and his co-workers have shown that there is a very close parallelism between the action of these drugs on trypanosomes and spirochaetes in man.

Toxicity tests. The International Conference on Biological Standards met at Geneva in 1925 and resolved that arsphenamine, its metallic derivatives, e.g., silver arsphenamine and its sodium salt, neoarsphenamine and its metallic derivatives and sulpharsphenamine should be standardised.

British test. (1) Neoarsphenamine 0.3 mgm. per gm. body weight is injected in five mice. If not more than one mouse out of 5 dies in three days the batch is passed for issue, if more than two die it is rejected. (2) If two die on the first test, a second test is carried out with five mice and 0.4 mgm. per gm. is given from a fresh ampoule. If not more than two mice die it is passed for issue.

American test. Arsphenamine. In the official method prescribed by the Hygiene Laboratory of the United States Public Health Service, white rats weighing from 100 to 150 gm. are employed. For each toxicity test, not less than five rats are used, and at least 60 per cent. of the animals injected must survive at least 48 hours after injection of less than 120 mgm. per kilo. of body weight of arsphenamine. This

dose is about 12 times larger per kilo. body weight than that ordinarily administered to human beings in a single dose (0.6 gm.). The total arsenic content should not be below 30 per cent. nor above 32 per cent.

Neo-arsphenamine and sulpharsphenamine. The total arsenic content should not be below 18 per cent. nor above 20 per cent. The drug should be freely mobile in the ampoule and should be readily soluble in cold water. The rats must survive seven days after an injection of 240 mgm. per kilo. This is 16 times the dose given to adult human beings. In cases of sulpharsphenamine, silver arsphenamine and silver neoarsphenamine the maximum tolerated dose should not be less than 140 and 180 mgm. per kilo. body weight respectively, by intravenous injection. Generally the compounds are considered safe for human being if animal tests show that these medicaments are borne in doses at least ten times larger than the amount required to be given according to body weight.

German test. Of three sets of five mice each receives from three different ampoules 0.37 mgm. per gm. 70 per cent., *i.e.*, 11 out of 15 must survive. With 0.42 mgm. per gm. body weight 50 per cent. must survive.

Japanese test. Ten mice are used and two-thirds, *i.e.*, seven out of ten must survive with a dosage of 0.27 mgm. per gm. The Japanese and American tests are slightly more lenient than the German tests.

It may be emphasised again that toxicity does not guarantee therapeutic activity and highly toxic substances may be therapeutically inactive. The specimens should, therefore, be tested both as regards their toxicity and therapeutic activity before being placed on the market.

Besides the oxides, methyl alcohol which is used in their preparation also occurs as an impurity, but it is in such small amount that its toxic effects can be ignored. The same is true of inorganic impurities like sulphites, sulphates and sodium chloride which may be present. According to some, sodium chloride may be responsible for producing fever.

CHAPTER XXX

TOXIC EFFECTS OF ARSENIC COMPOUNDS

Acute poisoning. Inorganic arsenic, when taken by the mouth in large doses produces severe gastro-intestinal irritation, vomiting, painful profuse watery diarrhoea (rice water stools), suppression of urine, intense thirst, prostration and collapse ; even when given hypodermically the drug produces its action on the epithelium of the gut, producing fatty degeneration, necrosis and ulceration. The symptoms usually appear within half to one hour after it is taken by the mouth. In fulminant cases, the accumulation of blood from the general circulation into the splanchnic area on account of capillary paralysis, may produce collapse and death without producing any of the usual symptoms. At the post mortem the stomach and intestines are found inflamed and there are patches of softened mucous membrane. If the patient survives long enough, fatty degeneration of the liver, kidney and heart is seen.

Fatal doses of white arsenic vary with the solubility of the preparation. Five to 50 mgm. of the trioxide produce toxic symptoms, while 0.1 to 0.3 gm. are fatal, but recovery may occur after much larger quantities. It has been shown that coarseness or fineness of the powder is an important factor in its toxicity, a solution of the oxide being 500 times as powerful as the coarse powder in the production of emesis.

Chronic poisoning. The symptoms which appear first are loss of appetite, nausea, vomiting, colic, and mild diarrhoea ; swelling of joints, peripheral neuritis, weakness, tremors of muscles, ataxic gait, muscular atrophy, bronzing and patchy pigmentation of the skin, darting pains in the limbs and muscular paralysis may occur. Persistent capillary paralysis produces diarrhoea and cedema ; sensation may be dulled and blindness may be produced. The endothelium of the capillaries, later the intestinal epithelium and finally the cells of such organs as the liver, kidneys, and the heart undergo fatty degeneration. Arsenic is quickly absorbed and is slowly excreted ; it is therefore

a cumulative poison. Pigmentation of the skin, dermatitis and peripheral neuritis commonly occur in chronic poisoning.

Treatment of arsenic poisoning. Acute arsenic poisoning is usually fatal, and therefore treatment should be started as early as possible. Elimination of the drug by emetics, lavage with warm water or purgation should be tried at the first instance. Chemical antidotes are not of much value. Ferric hydroxide with magnesium oxide was long considered the best antidote, the ferric hydrate and arsenic forming an insoluble compound. It is now known that the antidote is not effective to the same extent as was believed and that its administration only gives a slightly smaller percentage of fatalities. In any case, as this antidote is harmless, it may be given a trial provided that it is promptly followed by effective evacuation.

Chronic arsenic poisoning does not require prompt and energetic treatment. The administration of arsenic in any form should be stopped. Rest in hygienic surroundings, a milk diet and alkalies are indicated. Symptomatic measures against vomiting, diarrhoea, etc., and stimulants whenever necessary may be exhibited.

Toxicity of organic compounds. Organic arsenicals such as salvarsan and its substitutes are usually injected in doses as high as can be tolerated and therefore toxic effects are not uncommon. These are generally due to three causes; in order of importance they are—

1. *Pathological states and susceptibility of the patient.* Fear, nervousness, endocrine disturbances, vagotonia, pathological changes produced by syphilis, non-syphilitic diseases, mercury, etc., play an important part. Natural or acquired hypersensitiveness to arsenical compounds is another important factor.

2. *Errors in method of administration.* Failure to make proper solutions, *e.g.*, making them over-acid or over-alkaline, use of defective saline solutions, excessive dilutions, intravenous injection, oxidation of the solution, emboli of the undissolved drug, cotton, air, etc., are factors of some importance.

3. *Properties of the drug itself.* The solutions may have toxic physical properties, agglutination of erythrocytes or

precipitation of plasma may occur or hæmolysis may be produced. Oxidation of the drug may occur or toxic impurities may be present.

With all these possible causes of toxic reaction it is not surprising that various undesirable symptoms are produced. Some degree of systemic reaction occurs in 0.5 to 15 per cent. of all injections, but although they are alarming they are not often dangerous. The fatality rate in a German clinic (1920) was reported to be 1 in 63,000 if the dosage was below 0.6 gm., and 1 in 3,000 if it was above. The danger can be reduced by using a reliable drug, proper technique and careful examination of the patient. The symptoms may be divided into three groups.

A. Immediate reactions. In the great majority of cases after intravenous injection of neo-salvarsan and sulfarsenol by the technically correct method no untoward effects are noticed. The first effect mentioned by the patient is a peculiar odour, and metallic taste. This effect is probably due to the circulation of the drug in the mucous membrane of the nose and salivary glands and is noticed soon after the injection. Chewing of flavoured gum or cloves during injection does away with this. Not infrequently the patient experiences a feeling of fullness in the head, and slight flushing of the face which may only last a few minutes or less; these are due to the action of the drugs on the vasomotor system and are less marked with neo-salvarsan and sulfarsenol than with salvarsan. Slight perspiration and a feeling of faintness may be noticed. Nausea and vomiting sometimes occur half an hour after the injection in neurotic patients. Intramuscular and subcutaneous injections rarely produce nausea and vomiting and the other symptoms are as a rule absent. The more severe immediate reactions are as follows:—

1. Acute physico-hæmoclastic reactions occur with salvarsan solutions, and these are due to errors in neutralisation and the symptoms are the result of widespread embolism and infarction, especially of the lungs, and cardiac dilatation; clumps of agglutinated erythrocytes are found in the heart and in the intima of blood vessels. During injection the expression of the patient's face becomes drawn, hiccough or short spasmodic cough may

develop. Dyspnoea and suffocation ensue, the pulse becomes rapid, feeble and irregular; pain and constriction in the chest occur due to emboli in the lungs; convulsions may occur due to emboli in the brain; no demonstrable symptoms are produced by embolism of the liver, spleen, kidney and other organs. Broncho-pneumonia and pulmonary embolism may develop after an interval. The patient becomes anxious, expresses a fear of approaching death; coma may follow from cerebral anaemia. The patient may recover within $\frac{1}{2}$ to 2 hours or die. The cause of this acute crisis is unknown though coagulation of the blood proteins has been suggested. There is no evidence to support this, but agglutination of red blood cells may occur *in vivo* as a result of injection of solutions of arsphenamine, and multiple emboli have been noted in the lungs.

The treatment in these cases, is to lay the patient flat on his back and to give 1 to 2 minims of 1 in 1000 solution of adrenalin intravenously; for less severe reactions give 0.5 to 1.0 c.cm. intramuscularly. Atropine sulphate 1/50 grain may be given intramuscularly for stimulating the circulation. Intravascular agglutination can be prevented by injecting arsphenamine with a protective colloid such as gelatine.

2. Acute vasoparetic reactions or 'nitritoid crises,' so called by Milton (1912) because the symptoms and lesions resemble the inhalations of amyl-nitrite. These reactions are produced by intravenous injection of many substances and are common among individuals suffering from symptoms of adrenal insufficiency or thyroid disturbances. They have been attributed to the disturbance of the sympathetic system, but it is more likely that they are due to the toxicity of the drug or abnormal changes in the capillaries or a combination of the two. The symptoms occurring immediately after or during injection are flushing of the face, dilatation of the pupils, increased pulse rate and dimness of vision. There may be pain in the gums and teeth. In more severe cases, the lips and tongue become swollen, there is a feeling of constriction in the throat and upper part of the chest and dyspnoea; a tingling sensation in the extremities, congestion of the conjunctiva and lachrymation are always present. The patient may fall, if standing when the re-

action comes on. In still more severe cases there may be urticaria, either limited to portions of the body or generalised over the limbs and trunk; profuse perspiration, vomiting, retching, loss of sphincter control and possibly loss of consciousness which may last several hours. These symptoms, though rare, occur in a certain percentage of cases after each injection. Silver salvarsan, unless injected very slowly, almost always causes vasomotor symptoms. The face becomes pale, the pulse feeble, and vomiting may ensue. In another type of reaction rigors and headache occur; it is more common after the first than subsequent injections. Occasionally vomiting is followed by severe diarrhoea a few hours after the injection. Herpes labialis may occur. In mild cases the patient may feel nothing but fright. The symptoms can all be explained by sudden dilatation of blood vessels especially the capillaries. Extreme cerebral and meningeal congestion may occur causing apoplexy. In mild cases there is only headache and vomiting and these soon pass off.

Although the symptoms described are very alarming they are rarely fatal. Cases of cardiac syphilis with aortic insufficiency and myocarditis are specially liable to develop alarming symptoms with sudden syncope after arsphenamine. In these cases cold sweats, gasping respiration, pallor, bradycardia and low blood pressure are associated with acute cardiac damage.

Various explanations have been suggested to account for the immediate vasomotor disturbances. As adrenalin relieves those symptoms, it was thought that insufficiency of the adrenal glands might be the cause. Another explanation is that a precipitate is formed. None of these hypotheses are supported by experimental data. The theory most favoured is that the symptoms resemble anaphylactic shock, and many of these certainly seem to be those due to liberation of histamine and histamine-like substances.

Treatment. If symptoms appear the patient is made to lie flat and adrenalin 0.5 to 1 c.cm. of a 1 in 1000 solution is given intramuscularly at once or it may be used as a prophylactic before the injection. Pituitrin may be given with adrenalin or by itself, atropine sulphate 1/50 gr. subcutaneously relaxes the bronchi

and relieves dyspnoea. In severe cases of coma give adrenalin intravenously. Ephedrine is said to be specially useful in preventing vasomotor paralysis. Fractional injection, *i.e.*, 1/10 of the dose an hour before the full dose, may be adopted as a prophylactic measure. In animals, injection of caesium eosinate prevents the symptom of anaphylactic shock and 15 c.cm. of a 6 per cent. solution prevents shock in man; neoarsphenamine may be dissolved in this solution. Sometimes symptoms of increased cranial pressure or tension headache occur. In these cases magnesium sulphate should be given internally or by rectal enemata to produce dehydration. If symptoms of encephalitis appear the pressure may be relieved by drawing cerebro-spinal fluid, and adrenalin may be given.

B. Early reactions. These generally start in 1 to 4 hours, but may occur within 24 hours after injection. There is fever, headache, protein or colloidal shock; accidents of injection such as phlebitis and thrombosis, also come under this heading. The kidneys may be involved and albumin and casts may be found in the urine.

Gastro-intestinal symptoms occur if injections are given soon after a meal. These are nausea, vertigo, headache, thirst, vomiting and diarrhoea. Symptoms usually stop in 12 to 24 hours but may continue for several days. Adrenalin is also beneficial in these cases. Protein or colloidal shock produce fever, perspiration, chilliness or even a rigor.

C. Late reactions. These occur from one day to several weeks after the injection. These are hæmorrhagic encephalitis, dermatitis, neuritis, Herxheimer's reaction and jaundice. Hypersensitiveness to these reactions may be acquired. It is not infrequently seen that patients who have one or more courses of arsenical compounds, suddenly or gradually begin to develop immediate or early toxic reactions after small doses, *e.g.*, nausea, vomiting, flushing, occurring immediately after injections. The skin tests are negative so that the effect is not cumulative.

Jarish Herxheimer's reaction. This type of reaction has been attributed to liberation of luetic toxins from spirochaetes killed by the drug. The luetic lesions especially of the trunk,

show bright red erythema lasting a few days. Generally they cause little inconvenience, but it is conceivable that analogous reactions in cerebral and hepatic gummata may be dangerous.

Cerebral symptoms. Hæmorrhagic encephalitis occurs especially after large doses or when ordinary doses are given in quick succession. The symptoms start 2 to 5 days after injection with severe headache, vomiting, weakness, œdema of face, muscular twitching, dyspnœa, epileptiform convulsions, clonic spasms and suppression of urine. Loss of deep reflexes, a positive Babinski sign and continued convulsions are some of the signs of involvement of the central nervous system. Post mortem examination shows numerous small hæmorrhages, but no evidence of softening of the brain tissue; the capillaries are filled with hyaline thrombi. The lungs, spleen, and kidneys are all congested but free from thrombi. Arsenic is said to be responsible for the production of these symptoms. Hæmorrhagic encephalitis, however, commonly occurs in the second stage of syphilis. In a few cases it has occurred after a single injection of arsenicals, but in the majority of cases after the second injection. Examination of the brain may show the presence of arsenic or not. The ætiology or hæmorrhagic encephalitis is probably the same as that of the acute vasoparetic reaction following injection of arsphenamine.

Dermatitis and allied reaction. These are the most annoying of all reactions and consist of rashes on the skin and mucous membranes. They are less common with organic compounds and their characters depend chiefly on the sensitiveness of the patient to the drug, the amount of arsenic given and the degree of skin reaction. The most common types are patches of urticaria, erythema and rarely purpura, sometimes there is only itching. The eruptions generally subside in a day or two. More persistent eruptions occur 6 to 10 days after administration, especially after intravenous injections. The severe type of reaction may turn into exfoliative dermatitis which is very serious, as death follows after its appearance in about 30 per cent. of cases. Various stages may be passed so rapidly that an initial urticaria or discrete erythema may become a confluent erythema in 24 to 48 hours; later it may turn vesicular and subsequently

pass on to exfoliative dermatitis. Arsenicals should therefore be discontinued if signs of skin irritation appear. Kolmer has classified these reactions into 4 groups.

1. Mild and early skin lesions consisting of simple erythematous rashes, urticaria, herpes, pruritus. These may be due partly to colloidal phenomena and partly to liberation of spirochaetal endotoxins—Herxheimer's reaction.

2. Severe and late skin lesions consisting of dermatitis and purpura. The former may consist of scarlatiniform erythema with desquamation, erythema multiforme (papular and vesicular), lichen-planoid or with acute exfoliation which may be simple, rheumatic or hæmorrhagic.

3. Mucous membrane lesions consisting of stomatitis, exfoliative ileocolitis, conjunctivitis, vaginitis and broncho-pneumonia.

4. Chronic and recurrent skin lesions such as fixed arsenical rashes, pigmentation and argyria, melanosis, hyperkeratosis of the palms and soles of the feet may develop.

Forms of eruption. 1. *Erythema*. This may vary from mild redness to deep redness with a purple tint. It blanches on pressure, appears first on the flexor surface of the limbs and trunk. It may be petechial or hæmorrhagic, but often it is either morbilliform or scarlatiniform, erysipelatoid or of a patchy character resembling a copaiba rash. The rash may be discrete and papular, though the urticarial form is more common; it may be accompanied by a pemphigoid eruption which is characterised by the formation of vesicles and blebs that leave considerable pigmentation behind.

2. *Exfoliative dermatitis*. This is preceded by an acute erythematous dermatitis and in a mild case it does not go beyond the erythematous stage. The infiltration is more noticeable on hands, feet and ears; vesicles or bullæ may form and rapidly rupture, thus producing areas of acute weeping dermatitis, marked redness of the skin, exfoliation, crusting and scabbing from the drying exudate. The whole body may be uniformly affected or exfoliation may be confined to certain parts especially the ears, scalp, armpits, groins and fold of the skin. There is œdema of the eyelids, conjunctivitis and photophobia. Fever, headache, faucial congestion and emaciation are present. Secondary infection may take place. There may be loss of the hair of the scalp, eyebrows and eyelashes. The main complica-

tions are glandular enlargement, abscess formation in the groins, broncho-pneumonia, cedema of the lungs, exfoliative vaginitis. Albuminuria may be present. When recovery occurs convalescence is protracted, the skin becomes thin and atrophic and assumes a brown tint.

3. *Chronic skin lesions.* Fixed arsenical exanthemata develops by the production of urticarial patches in the same situation leading to an elevated smooth plaques. Raynaud's syndrome with gangrene has been recorded. Fibrosarcoma at the site of injection of arsphenamine has occurred.

Pathology. The skin lesions are due to the direct effect of the arsenical compounds and not due to the syphilis itself, as they have occurred in non-syphilitic patients treated with arsenicals. Recent work by Osborne (1928) has shown that the skins of patients with dermatitis contain more arsenic than those without. It has been shown by micro-chemical methods that arsenic is deposited deep in the corium around the arterioles and capillaries, in the walls and lumens of the sweat and sebaceous glands, in their ducts and in the hair follicles and hair shafts. The arsenic is always extra-cellular and the amount present is proportional to the severity of the dermatitis. Pentavalent arsenic appears to have a special affinity for ectodermal structures, *e.g.*, the epidermis, sweat and sebaceous glands, hair, and relatively little affinity for blood vessels of the corium. Pentavalent arsenicals therefore produce mild dermatitis, keratosis, pigmentation, wrist drop and optic atrophy; while trivalent compounds cause severe dermatitis, encephalitis and purpura. The incidence of severe skin reactions is 1 in every 500 to 1,000 injections and sulpharsphenamine produces a somewhat higher incidence. Non-syphilitics may also develop it. The skin reactions are 2 to 3 times commoner in white races than in coloured races.

Post-arsphenamine dermatitis is now considered to be the result of direct sensitization to arsphenamine, to the products of its metabolism or to a state of general allergic instability or to a hypersensitiveness not necessarily absolutely specific for arsphenamine. Two theories have been advanced to explain this condition. The hepatotoxic explanation holds that the liver is damaged to the extent that it is unable to detoxicate arsphenamine when introduced or else causes an altered metabolism of the arsphenamine. Jaundice seems to be a very common accompaniment. Liver extract has been used in arsenical dermatitis with good results, and sodium-dihydrocholate sometimes prevents hepatic reactions or post-arsphenamine jaundice. These facts show the possible relationship. The second theory known as epidermovasculotoxic or vasoneurotic theory, accounts for the cutaneous reaction as a primary toxic effect on the involuntary or autonomic nervous system which causes excessive

loading of arsenic in the skin, and liver. ~~The circulatory system, particularly liver.~~ The circulatory system, particularly the walls of the blood vessels form the chief point of attack.

Treatment. Most cases of arsphenamine dermatitis present warning signs before the generalised dermatitis begins. In early cases, the treatment with arsphenamine should be guardedly continued by changing to a different type of arsenical, smaller doses, etc., before true allergic state develops. Physiologic solutions of sodium chloride, dextrose, gelatin, sodium thiosulphate and calcium have been added to the arsphenamine to render it less toxic. Clinical experience has proved that sodium thiosulphate is a very valuable detoxicating agent. Its mode of action is unknown but probably it transforms arsenic into a less toxic, less efficient and a less easily excretable product. On the other hand, some authorities believe that owing to the presence of the sulphydryl group, sodium thiosulphate changes the insoluble arsenic compounds developed in the skin into soluble forms. In order to avoid arsenical dermatitis it is advisable to combine sodium thiosulphate with arsphenamine. But once the dermatitis has set in, sodium thiosulphate fails to hasten the resolution; its value only lies in its use early in the disease. Fifteen grains (1.0 gm.) of sodium thiosulphate by the mouth 3 or 4 times a day is said to produce good results, but in severe cases it should be given intravenously in 10 per cent solution, starting with 0.3 gm. on the first day, then 0.45, 0.6, 0.9, 1.2 and 1.8 gm. on successive days. At the same time it is given by the mouth in 2 gm. doses twice daily in 120 to 200 c.cm. of normal saline. Thiosulphate is said to act by releasing the arsenic deposited in the skin and along the nerve trunks until gradual return to normal is observed. The excretion of arsenic is accelerated, the parchment-like condition of the skin disappears and the pigmented areas become normal. Beinhaner and Jacob (1928) are of opinion that Wassermann-fast syphilis is due in some cases to a saturation of the tissues by the heavy metals used in the treatment, or to arsenic-fast or mercury-fast strains of spirochaetes. In such cases sodium thiosulphate produces excellent results. They recommend a series of bi-weekly intravenous injections for 5 to 7 weeks, an average dose of

0.6 gm. of the drug being given at each injection. The patient also receives 15 grains (1.0 gm.) of this drug daily by the mouth at the same time. Sodium thiosulphate definitely alters the serum reaction in some cases of Wassermann-fast syphilis.

Thiosinamin has also been recommended intravenously in 3 grain doses in 10 c.cm. of sterile water but it may produce digestive disturbances, lassitude and fever. Intramuscular injections of intramine in doses of 2.5 c.cm. of a 1.0 per cent. emulsion are beneficial; as many as 12 injections may be given.

Liver therapy. Based upon the hepatotoxic theory, some workers have used injections of liver extract in the treatment of arsenical dermatitis with good results. It is given in doses of 5 to 10 c.cm. intramuscularly, three times a week. The therapy stimulates the disturbed function of the liver, cures chronic arsphenamine intoxication and prevents further manifestation of arsphenamine sensitisation.

Other effects. An intense necrotic type of enteritis has followed treatment with arsenicals and mercury, leading to perforation and fatal peritonitis. Severe parenchymatous degeneration of the kidneys has been known to occur after arsphenamine. A true syphilitic nephritis is well known. Arsphenamine in rare cases may produce aplastic anaemia with degeneration of the bone marrow. There may be bleeding from the gums and mucous membranes in many cases and the red cell count may be reduced to 80,000 and haemoglobin to 13 per cent., the leucocyte count is also reduced. Post-mortem examination shows complete aplasia of the bone marrow and broncho-pneumonia with a poor cellular reaction.

Syphilitic and arsenical jaundice. The intensity of jaundice may vary from a transitory jaundice to acute yellow atrophy of the liver. It may be early or benign, late or severe, and lastly acute yellow atrophy may result. Early jaundice commences within a few days, sometimes within a few hours of the injection. It may come on after the first injection or after any subsequent injections. There may or may not be any constitutional disturbance, but that does not mean that the liver has not been damaged. Cases have been recorded with initial transient jaundice but some months later the patient has died of acute yellow atrophy of liver. Late jaundice is a very serious condition. It is accompanied by fever and usually occurs after many

injections (one or two courses) and is believed to be more commonly caused by neo-salvarsan, though there are no data to support this belief. Jaundice is generally intense and unless there is acute yellow atrophy of the liver, the patient may recover. In the late type of jaundice symptoms are not so severe as in acute yellow atrophy. The jaundice, from the beginning, is intense but non-febrile. Then suddenly symptoms of acute hepatic insufficiency, such as fever, rigors, vomiting, delirium and other nervous symptoms supervene and the patient dies of coma. Kolmer has classified jaundice into four groups according to its ætiology.

1. Due to arsenic, by production of fatty degeneration, hepatitis or obstructive jaundice produced by gastro-enteritis. That the arsenicals damage the liver can be shown by the lævulose and blood lipase test, even therapeutic doses produce structural alterations, and the phenol-tetrachlor-phthalein test shows signs of insufficiency after a series of doses or courses. The interesting fact in connection with acute yellow atrophy is the long latent period usually intervening between the last injection and the onset of symptoms. With trinitrotoluene, jaundice may occur 2 to 10 months after exposure. It has been suggested that this delay is due to the fact that arsenic is stored partially in the body. If for any reason these depots are rapidly depleted, a large amount of arsenic is liberated and the liver is attacked.

2. Due to syphilis alone. This may be mild or severe and the pathological changes are perihepatitis, diffuse hepatitis or gumma.

3. Due to arsenic and syphilis. This is considered to be a form of Herxheimer's reaction; syphilitic infection of the liver is intensified as a result of administration of arsenicals. Arsenicals may also stimulate a bacterial infection of the liver.

4. The immediate predisposition to jaundice is neither due to arsenic nor syphilis of liver, but in the majority of cases to summation of the changes produced by the disease and the arsenicals, and it is possible that the administration of mercury may help in intensifying the hepatic damage. Jaundice is the result of combined hepatic disturbances and cholangitis produced by syphilis and arsenic, while in other cases it may be due to Herxheimer's reaction when latent spirochætes in that organ have been stimulated into renewed activity. Experiments on dogs have shown that with chloroform the amount of damage produced in the liver is variable, but if living bacteria are injected at the same time all grades of hepatic damage from acute atrophy to cirrhosis may occur. Other infections such as Weil's disease (*Sp. icterohæmorrhagica*) may be etiological factors. Liver function tests such as the phenol-tetrachlor-phthalein test are useful, as syphilitic

hepatitis is not usually suspected till jaundice and the accompanying symptoms appear.

Treatment of jaundice. Rest in bed, mild laxatives, carbohydrate diet which increases the resistance of the liver, with no fats and little proteins are recommended. Milk may be given and the patient is advised to drink plenty of water. When jaundice is clearly due to syphilis, give anti-syphilitic treatment with arsenicals, mercury or bismuth compounds; but if due to arsenic injections these should be immediately stopped. Intravenous injections of sodium thiosulphate, thiosinamine or con-tramine (diethyl-ammonium diethyl-dithiocarbamate) have been recommended.

Many fatalities attributed to arsenicals are really due to advanced pathological changes produced in the internal organs by the disease in which these drugs either should not have been given at all or only in very small doses. Women are more likely to develop reactions than men. Mild reactions such as nausea, headache, fever, diarrhoea, etc., are more common among them; the incidence of jaundice is also higher. Severe and fatal reactions are more common among men; children are more tolerant to arsenicals. The incidence of reaction according to Kolmer (1926) is generally higher after 5 or more injections than after the first injection. There is also a greater tendency to reaction during the second or subsequent courses. It is probable therefore that the effects are due to the accumulation of arsenic in the liver and other organs, to the production of tissue injury or to interference with the metabolism or excretion of these compounds. In some cases an allergic sensitiveness is acquired for the drugs.

Meirowsky (1920) showed that when the dose of neo-salvarsan exceeded 0.6 gm. the death rate went up considerably and hence he recommended 0.6 gm. to be the maximum dose. The death rate was much less with neo-salvarsan than with salvarsan. Strong solutions of salvarsan and sulfarsenol are directly hæmolytic *in vitro* for washed corpuscles, but they are much less so in the presence of serum, and intravascular hæmolysis is not therefore very likely to occur. Weak solutions of salvarsan such as 1 in 5,000 are said to have an antihæmolytic effect. Concentrated solutions, especially if injected rapidly, produce fatal results. Neo-arsphenamine has little hæmolytic action unless dissolved in water. Atoxyl, tryparsamide and other arsenicals are less hæmolytic in saline solutions and only slightly hæmolytic in water. It will thus be seen that hæmolysis can to a certain extent be prevented. The susceptibility of the erythrocytes to hæmolysins differs in different individuals and even a small amount of hæmolysis may produce symptoms resembling protein shock.

Nervous reactions. Numbness of the fingers and the soles of the feet may occur. As these symptoms frequently forecast the onset of dermatitis the injections should be stopped. As a rule these are not accompanied by pain but this may occur and polyneuritis may be produced followed by paralysis. Neoarsphenamine is said to have produced more cases of paralysis than arsphenamine. Sometimes injections are followed several weeks or months later, by severe nervous manifestations, *e.g.*, epileptiform convulsions. They occur also with mercury and Ehrlich suggested that they are due to incomplete destruction of the parasites. The optic and auditory nerves are not affected by trivalent compounds but atoxyl and tryparsamide (pentavalent compounds) produce retrobulbar neuritis and transient dimness of vision or amblyopia. Young and Lævenhart (1924) showed that arsenicals with an amino group or a substituted amino group in the para position to the arsenic, *e.g.*, atoxyl, produce optic atrophy in the rabbit. Organic arsenicals with the amino group in the ortho or meta position to the arsenic on the other hand, produce no optic atrophy. Herxheimer's reaction occurs in secondary syphilis especially if large doses have been given; small ascending doses of these compounds do not produce it.

Summary. The toxic symptoms produced by injections of organic arsenicals may be briefly classified as follows:—(1) Those occurring immediately, *e.g.*, flushing of the face, headache, lachrymation, oedema, dyspnoea, swelling of the lips, tongue and eyelids, nausea, vomiting and retching, unconsciousness and very rarely death (anaphylactoid or nitritoid crises). (2) Those appearing within 24 hours, *e.g.*, chilliness, rigors, headache, vertigo, diarrhoea, and rise of temperature. (3) Those observed after 24 hours, *e.g.*, epileptiform convulsions, dilation of the pupils, loss of reflexes, coma and rarely death. In addition there may be eruptions on the skin, exfoliative dermatitis (complicated with broncho-pneumonia and septicæmia), jaundice (early, late and acute yellow atrophy), epilepsy or hæmorrhagic encephalitis. Acute yellow atrophy often supervenes on late jaundice. Rare lesions are acute hæmorrhagic nephritis, ulcerative enteritis and aplastic pneumonia. (4) Complications now regarded as relapses of syphilis, are due to

spirochaetal toxins suddenly liberated. These include affections of the nervous system, deafness, cranial nerve palsies, etc.

Pathological changes produced by organic arsenicals. These changes were studied in animals. The type of changes produced is the same with all the trivalent and pentavalent compounds, some being more toxic than others. Tissue changes are chiefly due to the arsenic constituent and consist of, (1) congestion of capillaries and consequent serous exudation and minute hæmorrhages and (2) parenchymatous degeneration of organs and necrosis. If death occurs at once or within a few hours, there is widespread intense hyperæmia of the brain and meninges, lungs, liver, kidneys and other organs, with extensive thrombosis and plasma precipitates. Small capillary hæmorrhages are found in some organs, but degenerative lesions are not produced unless the animals survive a few days. In human subjects, where death occurs within 24 hours after accidental administration of acid solution of salvarsan, advanced degenerative lesions are found in the liver, kidneys and other organs. The majority of deaths in human subjects have occurred after several doses have been given, death being due to chronic rather than acute poisoning. In Europe, salvarsan fatalities are mostly ascribed to hæmorrhagic encephalitis but in the United States they have been put down to degenerative changes in the liver and kidneys.

In rats irregularly distributed areas of degenerative changes with lymphatic infiltrations are found in the myocardium after 10 or more small doses. Such changes in the human heart therefore should not be attributed to syphilis. Vascular lesions are especially marked in the lungs. After a single dose, when examined two days after the injection, marked congestion, small thrombi of coagulated erythrocytes are seen with areas of scattered congestion and extravasation of red corpuscles in the air sacs. After injection of numerous small doses the capillaries are found to be tortuous and densely packed with erythrocytes. The walls of the air sacs are thickened, the whole picture suggesting passing congestion and capillary oedema; there are no pleural changes.

The changes produced in the liver are of interest specially in relation to jaundice. A single large dose in rats produces extensive areas of coagulation necrosis involving all parts of the lobule, particularly the middle and the central portions. Rats succumbing after 2 days show the same changes as in acute yellow atrophy. After 10 or more small doses peripheral fibrosis with small areas of focal necrosis is noticed. The kidneys after a single large dose show congestion of the cortex, minute interstitial hæmorrhages and cloudy swelling, especially of the convoluted tubules. After repeated small doses the kidney changes are not marked. Clinically it has been noticed that kidney changes are less likely to occur with arsenicals than with mercury and bismuth compounds. In the supra-renals, after a large single dose, great reduction in the lipid and chromafin contents is produced. In the spleen large single

doses produce areas of coagulation necrosis while small doses produce no marked changes. Kolmer and others (1922) found no decrease in the adrenalin content of the suprarenal glands after injection of arsphenamine in therapeutic doses.

It will be seen from the above that repeated injections of small doses are much less toxic than single large dose, and the small changes that are produced in the organs are quickly made good. It is likely that 'nitritoid crises' are due primarily to the direct action of arsenic on the capillaries in individuals hypersensitive to arsenic. The skin eruptions such as urticaria, and exfoliative dermatitis, may be due to the direct action of arsenic on the capillaries and excretory glands of the skin, while jaundice is ascribed to necrosis of the liver cells by arsenic or to a phenomenon resembling Herxheimer's reaction. The susceptibility of the individual is a very important factor and so also are the pre-existing pathological changes produced by disease. For this reason, treatment of chronic syphilitics with organic arsenicals presents a much more difficult problem than cases of early syphilis.

Cautions and contra-indications. The only real contra-indication is hypersensitiveness to arsenic. Individuals who develop acute reactions, dermatitis and jaundice are bad risks and in these cases other drugs should be tried. Sometimes the substitution of one compound for another may avert such reactions. In minor cases of dermatitis if a beginning is made with a small dose and it is gradually increased, severe reactions may be avoided. A sharp look-out must be kept for urticaria, fleeting erythema, itching of the palms, etc., as these give a warning that more severe reactions may follow. Cases of jaundice are also bad risks and very great care should be taken in giving arsenicals if previous injections have caused it.

Organic arsenicals should be given with caution in cases of emaciation, malnutrition, in diseases of the heart and blood vessels (syphilitic aortitis and myocarditis), in tuberculosis with hæmoptysis, in affections of the brain and meninges, in advanced cases of diabetes and nephritis, and in old and feeble persons of very advanced age. Arsenic should not be given where vitality is very low as a result of acute manifestations of syphilis. In syphilis of the optic nerve pentavalent arsenicals should never be given, while trivalent compounds should only be tried in small and ascending doses. According to some authorities tryparsamide may be given safely when the optic

nerve is diseased provided the doses are small and carefully regulated.

Prophylaxis of toxic reactions. The measures taken have been divided into three groups.

1. *Those referable to the patient.* Allay fear and nervousness; if constipation is present it should be relieved; the injection should be given on an empty stomach, preferably in the morning; the urine should be examined previously in all cases, especially when mercury and bismuth are also being tried; the functional capacity of the liver may be tested in selected cases. The first dose should be small, $\frac{1}{4}$ to $\frac{1}{2}$ of the usual dose; this tends to increase the tolerance of the individual. In long-standing cases, give mercury or bismuth first or very small doses of arsenicals to prevent Herxheimer's reactions. In women the injections should not be given during the menstrual period and special care should be exercised when pregnancy exists, as abortion may take place. When giving pentavalent compounds special attention should be paid to the eyes to guard against toxic amblyopia. The injections should be given deep into the muscles and not into the fatty tissue. In patients likely to develop vaso-paretic symptoms 1/100 to 1/50 grain of atropine sulphate should be given half-an hour before the main injection. Two to 8 minims of 1 in 1,000 adrenalin intramuscularly before the injection prevents acute vaso-paretic reactions. Adrenalin is the most useful drug to cope with 'nitritoid crisis.' Injection of calcium salts either prior to or in conjunction with salvarsan or neo-salvarsan injections is said to prevent the toxic effects of the drug. Calcium chloride dissolved in distilled water is usually given intravenously, but it may also be administered orally.

2. *Those referable to the preparation and administration of solutions.* Use freshly distilled water or saline free from organic matter. For dilute solutions (50 c.cm. or more) use 0.5 per cent. saline in preference to water. Filter all solutions. After neutralisation allow arsphenamine solutions to stand for 10 to 20 minutes before injection. Injections should be given slowly. New rubber tubing should be avoided.

3. *Those referable to the drug.* Avoid products over two years old and all cracked ampules should be thrown away.

If there is suspicion of a crack dip the ampoule in alcohol which will find its way in if there is a leak. Before injection carefully verify the drug which is going to be injected. Solutions should never be given unless they are brilliantly clear; cloudy solutions produce abdominal pains and immediate syncope. If necessary they should be filtered.

Keeping properties and media for solution. Salvarsan and the allied compounds should be kept sealed in ampoules in vacuo. It is better to use fresh rather than old specimens. Solutions of the compounds can be kept for six months or longer without physical changes or increase of toxicity if the oxygen is rigidly excluded. The Hygienic Laboratory of U.S.A. has placed a limit of six months on them from the date of preparation. Freshly distilled water should be used for making solutions. When concentrated solutions of neo-salvarsan are employed they should be dissolved in distilled water, but if dilute solutions of salvarsan are used the drug should be dissolved in 0.5 per cent. saline solution prepared from chemically pure sodium chloride. A 5 per cent. solution of glucose as a medium for dissolving these compounds reduces the toxicity by preventing oxidation in solution, at the same time it does not reduce their therapeutic activity. In 0.5 to 2 per cent. gelatine solution the toxicity of these compounds is said to be reduced, but as this gives rise to reactions such as malaise, chilliness, etc., it is not recommended. Solutions of salvarsan in water heated up to 60° to 70°C and then cooled do not show any increase in toxicity; neo-salvarsan and sulfarsenol are best dissolved in cold water. It has been clearly established by experiments that it is better to use dilute solutions of salvarsan (0.4 gm. in 20 to 25 c.cm.) while concentrated solutions (0.9 gm. in 2 c.cm.) of neo-salvarsan and sulfarsenol do not do any harm when given intravenously. It has been pointed out that shaking the solution in air, even for a few seconds, increases the toxicity of all these compounds by oxidation to arsenoxide, but if contact with air is prevented by means of stoppered bottles, solutions may be safely kept for a few hours before injection; some say they may be safely kept for 24 to 48 hours. Excess of alkalinity or acidity of the salvarsan solution are both dangerous.

CHAPTER XXXI

BISMUTH AND ITS DERIVATIVES

Bismuth compounds were used as cicatrising agents in the treatment of cutaneous lesions as early as the 17th century, and towards the end of the 18th century they were given internally for gastro-intestinal disturbances; bismuth oxide was used for dressing wounds and ulcers. Balzar (1889) carried out a series of experiments on dogs to test the toxicity of bismuth compounds with a view to their employment in syphilis. He first successfully tried bismuth ammonium citrate in human syphilis. Robert and Sauton (1916) tried bismuth preparations in the treatment of spirochaetosis of fowls and found them to be very efficacious. Kolle and Ritz (1918) injected colloidal bismuth intravenously in syphilitic rabbits with beneficial results, but did not pursue the subject further. Sazerac and Levaditi (1921) carried out systematic research in the subject and found that in experimental syphilis of rabbits bismuth compounds had a well-marked curative action. They tried intramuscular injections of tartro-bismuthate of sodium and potassium (trepol) in syphilis in man and found that though the injections were painful, the drug produced rapid cicatrization of the lesions of this disease. Further trials by Fournier and Guenot (1922) showed that primary chancres healed rapidly, secondary lesions were inhibited and early secondary and tertiary lesions disappeared after 10 to 12 intramuscular injections of bismuth. In trypanosome infections the action was not marked.

These findings led gradually to the introduction of bismuth in the treatment of syphilis. As an adjunct to the arseno-benzene derivatives, bismuth is now recognised as a drug of considerable value and has replaced mercury in the chemotherapy of syphilis. It will therefore be of interest to consider the subject in detail, with special reference to the new contributions that have been made in connection with its pharmacological action and toxicological properties.

Pharmacological action. Like arsenic and antimony, bismuth in very high dilutions exerts a markedly toxic action on certain pathogenic protozoa; 1 in 200,000 will kill some of the organisms *in vitro* and it is possible that in the body this action may take place even in lower concentrations. Like atoxyl, these compounds only become active when incubated with liver extract and to a lesser extent with extracts of other tissues. The bactericidal properties of bismuth compounds have not been thoroughly studied, but their action in checking undesirable fermentation in beer worts was known long ago. Common bismuth salts like the subnitrate and the subgallate, etc., are decomposed by water to a greater or lesser extent, and can exert a mild but effective and prolonged antiseptic action.

External. Soluble bismuth salts are not used externally. The insoluble basic bismuth salts are largely used as dusting powders on inflamed surfaces. Their action is mainly mechanical as protective, drying and dusting powders. Applied to wounds, they dry secretions and form a protective covering so that the wound heals under an aseptic scab. A small amount of bismuth goes into solution and acts by exerting an astringent and antiseptic action. Sometimes absorption from the wounds and raw surfaces may be very rapid giving rise to symptoms of poisoning.

When applied to the unbroken skin in the form of inunctions, bismuth does not exhibit any curative action in syphilis. Cutaneous syphilitic lesions are not affected by the local application of bismuth.

Internal. Bismuth compounds have the reputation of being antacids. This effect is partly due to diminution of gastric secretion and partly to neutralisation of the gastric acidity. So far as the subnitrate is concerned this is undesirable as it does not fix the free acids to any great extent in the stomach. In the intestines both the subnitrate and the subcarbonate neutralise the sulphides of alkali metals and hydrogen sulphide, which produce irritation and increased intestinal peristalsis; these bismuth salts thus act as gastro-intestinal sedatives in inflammatory conditions of the gut. Further they coat the surface of the inflamed mucous membrane and allay irritation by preventing the irritant gases and fluids from coming in contact with the mucosa. They also exert a certain amount of antiseptic and astringent effect and are therefore prescribed in diarrhoea. Basic salts of bismuth are among the most effective of the non-irritant intestinal antiseptics. Subcarbonate of bismuth is preferred to subnitrate as the latter is converted into nitrous acid by reduction in the intestines. The use of soluble bismuth salts in irritative conditions of the gastro-intestinal tract is irrational since they are absorbed more readily and lack the soothing qualities of the insoluble preparations. In the gut bismuth salts are converted into sulphide, which is black in colour; it may form crystals looking like hæmatin and may be mistaken for it.

Circulation and respiration. After intravenous injections, even in small doses, there is a fall of blood pressure, partly due to depression of the vasomotor centre, but chiefly to the direct effect on the heart which becomes slow and irregular. The respiration is accelerated at first, but later depressed. The blood shows a mild and temporary leucocytosis after injections of bismuth salts. Neutrophiles and eosinophiles are increased at first, followed by an increase of lymphocytes. In some cases erythrocytes are increased while in others there is destruction of the red corpuscles. Punctate basophilia may occasionally occur. These effects appear to be due to the action of bismuth on the bone marrow which is stimulated temporarily by small doses, while in large doses toxic effects are produced.

Kidneys. All bismuth compounds tend to increase the output of urine and thus promote their own excretion. The administration of water and sodium chloride, etc., hastens the excretion of bismuth. A high chloride dietary would, therefore, favour the efficiency of bismuth medication by helping the mobilisation of the metal from the tissues. The diuretic action of bismuth may be made use of in the treatment of œdema and anasarca. Its action has been found to be well sustained and useful in the removal of large quantities of fluid.

Central nervous system. In frogs the symptoms are those of stimulation of the spinal cord and medulla oblongata, followed by depression and paralysis. In mammals, intravenous injections of large doses of bismuth act chiefly on the central nervous system producing violent clonic and tonic convulsions, followed by short intervals during which the movements are weak and inco-ordinated.

Absorption of bismuth. Only very minute quantities of bismuth are absorbed from the alimentary canal. This is shown by the fact that poisoning never results even when large doses of bismuth compounds are given by the mouth if the mucous membrane is intact. If there is solution of continuity and ulcers are present, the drug may be rapidly absorbed.

Absorption is so slow and uncertain from the gastro-intestinal tract that this route of administration is not employed for the treatment of such diseases as syphilis where a systemic action is desired. Absorption of bismuth from the skin in any form is not demonstrable as in the case of mercury. Hypodermic injections are too irritant and are not advisable. Intravenous injections of most of the bismuth compounds are not considered safe. This can be judged from the fact that while intramuscularly a rabbit can survive 200 mgm. of bismuth salts per kilo. body weight, 5 mgm. is sufficient to kill it if given intravenously. Intramuscular injection is therefore the only mode of administration and is universally adopted.

All bismuth products are tissue-soluble though in varying degrees. Absorption from the site of injection starts promptly but does not go on at the same rate in every case. This has been studied carefully by chemical, roentgenological and histological methods in animals, and also clinically in human beings. Saturation of the body with bismuth is more rapid, uniform and satisfactory with the soluble than with the insoluble salts. Absorption of the drug has been found to depend on several factors:—(a) the solubility of the original compound, (b) the site of the injections, (c) the number and frequency of the injections and (d) the dosage of bismuth employed. The solubility of the compound appears to play a most important part in absorption. Sollmann has grouped the bismuth preparations according to the degree of their solubility in different vehicles, as follows:—

Group I. Those soluble in water and in water-miscible media such as sucrose solution and ethylene diglycol. Water-soluble compounds suitable for this purpose are the double salts, sodium or potassium citrate or tartrate; sodium iodo-bismutite (iodobismutol) and sodium bismuth thioglycollate (thiobismol).

Group II. Those soluble in oil, including basic bismuth salts of certain organic acids (biliposol, cymbismol) and quiniobin, an oil-lecithin solution of bismuth-iodoquininate.

Group III. Oil suspensions of water-soluble compounds, especially the potassium bismuth tartrate

Group IV. Oil suspensions of insoluble (or sparingly soluble) compounds, such as bismuth iodoquininate (quinby), salicylate (subsaliolate), benzoate and oleate and metallic bismuth.

Group V. Watery suspensions of insoluble compounds, such as bismuth hydroxide (Lomholt's magna), metallic bismuth (neotrepol), and semicollodial bismuth (bismol).

The first group of bismuth compounds is most easily absorbed, though some compounds of this group tend to get precipitated by interaction with the tissue fluids at the site of the injection. Oily solutions cannot come intimately in contact with the tissues, produce much less irritation locally, and are apt to get encapsulated before absorption is completed. Hence they are not absorbed so well as the watery solutions but the process of absorption goes on for a long time and is obviously advantageous when prolonged effect is sought.

Fate of bismuth in the body. After absorption, bismuth like antimony, is widely distributed in the tissues of the body but in unequal amounts. After intramuscular injections bismuth can be detected in the blood in fairly high concentration in the plasma, though the corpuscles also contain it in negligible amounts. The concentration is highest in the kidneys indicating that the kidneys can store bismuth. The long bones, liver, lungs, spleen, skeletal muscles and the brain also contain traces of the drug. The placenta is permeable to bismuth and it can be

found in the foetus. Demelin (1922) was able to detect bismuth in the cerebro-spinal fluid of patients treated with intramuscular injections of 0.2 gm. of 'trepol,' but Jeanselme and his co-workers (1924) with a delicate method, capable of detecting bismuth in 1 in 1,000,000 dilution, failed to detect it in 31 patients who had intravenous injections of bismuth. There is no doubt however that there is improvement in the condition of many neuro-syphilitics following bismuth injections and minute quantities probably reach the central nervous system.

Bismuth appears to have the same distribution as other heavy metals, such as mercury and lead and is chiefly found in the organs concerned in its elimination. Owing to its widespread distribution syphilitic lesions of different parts of the body improve after bismuth therapy.

Excretion. Although some bismuth is stored in the liver and other organs, the greater part is eliminated by the kidneys, liver and intestines, only traces occur in sweat, milk and tears. The main channel of excretion appears to be the kidney, only one-twelfth to one-eighth of the bismuth appears in the faeces. Bismuth appears in the urine within 18 to 24 hours after intramuscular injection of 'trepol' and excretion is continued for 20 to 25 days after a course of treatment in which 2.0 to 2.5 gm. of this substance have been injected. After intravenous injections, bismuth can be detected in the urine in four hours. Sometimes the urine when voided is discoloured or becomes so on standing. In the latter case this is due to the formation of bismuth sulphide by the action of bacteria. The diuretic action of bismuth salts has already been referred to.

In human poisoning, bismuth is found mainly in the stomach and kidneys, and a little in the liver. Autopsy shows the caecum, adjoining colon and appendix stained black with bismuth sulphide, which is deposited on the mucous membrane in the capillary vessels and lymph spaces. The small intestines are clear.

CHAPTER XXXII

THERAPEUTIC USES OF BISMUTH

Bismuth subnitrate and carbonate are valuable drugs in the treatment of inflammatory conditions of the intestines, in diarrhoeas and in gastro-duodenal ulcers. They should be given in large doses, 30 gr. (2.0 gm.), as a powder or in suspension, by itself or in association with magnesium oxide or sodium bicarbonate on an empty stomach. Bismuth compounds act well in gastralgia and hyperchlorhydria. Bismuth subcarbonate or salicylate in 5 to 10 gr. dose several times a day in gelatine capsules is very useful in combating flatulence. In combination with alkalies they are also used as accessories to the emetine treatment of amoebic dysentery. They also ameliorate symptoms of this disease by their inhibiting action on the peristaltic movements of the intestine by neutralising the alkaline sulphides and sulphuretted hydrogen present there. They are used in chronic ulcers of the skin and in the treatment of deep-seated sinuses. The nitrate or carbonate of bismuth, mixed with vaseline in 30 per cent. strength is injected into tuberculous and other sinuses with the object of producing healing effects by cicatrization. They are however liable to cause poisoning if the sinuses are very extensive.

Syphilis. The bismuth treatment of syphilis is one of the noteworthy recent advances of therapeutics. The spirochæticidal properties of the organic and inorganic compounds of bismuth have been thoroughly tested and they are being largely used at present in the treatment of syphilis, especially by the French physicians. Robert and Sauton (1916) found that in spirochaetosis of fowls (*S. gallinarum*) doses of 0.2 to 0.03 gm. per kilo. intravenously or intramuscularly had a markedly beneficial effect. Doses of 0.005 to 0.015 gm. intravenously and 0.06 to 0.07 gm. intramuscularly injected 6 hours after infection invariably cured the animals. Similar results were obtained by Sazerac and Levaditi (1921) in experimental syphilis in rabbits, and by Fournier and Guenot (1924) in man. Bismuth

compounds such as 'trepol' are found to possess spirochæticidal activity of a very high order. This will be appreciated from the fact that a concentration of 0.2 mgm. in one litre of blood is sufficient to produce an antisyphilitic effect. A single therapeutic dose is five times smaller than the single maximum tolerated or toxic dose, i.e., the chemotherapeutic index is 5, which is very much higher than that of mercury compounds, but not so high as that of the organic arsenicals.

All forms of clinical manifestations of syphilis respond to bismuth treatment. The effective curative dose is 4 to 5 mgm. per kilo. per course of two or three courses. In primary and secondary syphilis a few centigrammes of 'trepol' produce rapid disappearance of spirochætes from the lesion, and cicatrization. Spirochætes disappear from the chancre in 24 to 56 hours, the chancre is healed in 4 to 10 days, and enlarged lymph glands in the neighbourhood of the chancre disappear. Rapid disappearance of mucous patches occurs after administration of bismuth compounds; a previously positive Wassermann reaction may become negative under treatment but not so rapidly as with the arsenicals. With colloidal bismuth mucous papules become cicatrized and treponema disappear after the first or second injection. Headache, fatigue and pains in the bones frequently cease after a few injections. In the tertiary stage of the disease bismuth is also useful, gummata disappear and also chronic encrusted ulcers of long standing and ulcers of the palate heal up rapidly. Cases which are resistant to mercury and arsenic, sometimes do better with bismuth. According to Meyer and Corbett (1923) bismuth appears to be less effective and slower in action than salvarsan but more effective than mercury. After treatment with arsphenamine no living spirochætes can be detected after 24 hours, whereas after treatment with bismuth, living spirochætes do not disappear for 3 to 4 days in the mucous lesions. Levaditi and Fournier (1928), however, state that liposoluble bismuth preparations act as rapidly as the arsenicals in destroying spirochætes. Bismuth has definite advantages over mercury and arsenic in some respects. It is not so depressing as mercury, old and debilitated patients tolerate it better than arsenic, and it can also be given for a much

longer period than either mercury or arsenic. Bismuth is specially effective in syphilitic lesions of the eye. In congenital syphilis the action of bismuth is more marked; although it is not so rapid as the arsenicals, it is more certain. That reinfection after bismuth therapy has occurred shows that the sterilization produced by it is definite and permanent. Simultaneous treatment with arsphenamine is not necessary for clearing and healing of acute lesions, or for sterilisation of lymph glands, as bismuth is effective by itself. Combined treatment however is desirable to cut short the length of treatment and to diminish the discomfort and inconvenience of the patients. The combination of bismuth with arsenicals is preferred by many authorities to the combination of mercury and arsenicals because the former is more effective. The usual course in man is $1\frac{1}{2}$ to 3 gr. (0.1 to 0.2 gm.) of sodium potassium tartro-bismuthate or potassium tartro-bismuthate in sterile olive oil or almond oil, weekly or biweekly, until 30 to 40 gr. (2 to 3 gm.) have been given. A six weeks' course of bismuth is followed immediately by a course of arsenicals, followed by a few months' rest. The courses of bismuth and arsenic are again repeated, the progress of the patient being carefully watched with serological tests. Harrison (1929) however thinks that there is no definite evidence of the superiority of bismuth over mercury and that either of the two metals may be used to supplement the arsenic treatment of syphilis.

Effect on serological reactions. The development of a positive reaction in case of primary sero-negative syphilis treated with arsenicals is very rare; but with bismuth treatment a weakly-positive reaction may develop. After one month's treatment of primary and secondary sero-positive cases more sero-negative cases are obtained with arsenicals than with bismuth preparations. Cases of positive Wassermann reaction, which are uninfluenced by arsenic or mercury, are unaffected by bismuth also. In congenital syphilis there is more chance of the reaction becoming negative with bismuth than with arsenicals. The action of bismuth is considered by some to be inhibitory rather than curative.

Neurosyphilis. Syphilis of the nervous system is not frequently benefited by arsenic preparations; in these cases bismuth preparations are useful. Their efficiency in the neuro-manifestations appears to be superior to that of the arsphenamines and equally as good as that of mercury. Tabetics are generally benefited by bismuth compounds, symptoms of gastric crisis and urinary incontinence may be ameliorated and ataxia may show some improvement. Insoluble preparations in the form of intramuscular injections are recommended in these cases, especially when mercury is not well borne. Bismuth is proving more useful than mercury in the treatment of meningeal neurosyphilis with headache. Mercury was the chief drug used in the treatment of neurosyphilis and even now it is advised by the neurologists in combination with arsenical treatment. The reason why mercury fails in general paralysis of the insane is not known but probably it does not penetrate into the nervous tissues. Even bismuth compounds often do not produce much improvement in this condition.

Kolmer has summed up the position of bismuth in the treatment of syphilis as follows:—"Bismuth has established for itself a permanent place in the treatment of syphilis by reason of its low toxicity for the body associated with marked spirochaeticidal properties; it is specially indicated in the treatment of acute syphilis when arsphenamine and its substitutes and mercury cannot be given, *e.g.*, in nephritis, jaundice, etc.; it is of value in the treatment of chronic syphilis and especially that of the central nervous system; it is usually well borne where mercury is not, and therefore serves as a valuable substitute for mercury in chronic syphilis when the latter cannot be given in adequate dosage. Otherwise it is unwise to use it as a substitute for either arsphenamine or allied compounds of mercury, until we know more of its final results. It is worthy of use in the treatment of syphilis in all its stages along with organic arsenicals and mercury, as a form of combination therapy, which is the keynote of success in the treatment of either acute or chronic syphilis. It is specially indicated in cases resistant or intolerant to arsenic."

Prophylactic effects of bismuth in syphilis. The value of mercuric chloride solutions applied locally after exposure to infection has been known for a long time. Experiments on apes and man have shown that inunction with calomel cream prevents development of the infection. In rabbits calomel in lanoline, vaseline, benzoated lard or wax base, proves efficacious up to eight hours after inoculation.

Stovarsol is known to protect monkeys from syphilitic infections for 2 to 7 days.

Bismuth, like mercury and arsenic, is also claimed to have a prophylactic value against syphilitic infections. It has been seen that in experimental syphilis bismuth acts definitely as a prophylactic and that bismuth medication protects rabbits from infection for a month or more. The prophylactic efficiency of iodo-bismuthate is claimed to be about twice the curative action. Apparently the best way of utilising this property of bismuth is to have some preparations which can be taken by the mouth before exposure, *e.g.*, glycerite of bismuth.

Brigham treated a number of patients suffering from syphilis with glycerite of bismuth, administered orally, with marked clinical and serological improvement. The dose administered is usually 20 minims (1.3 c.cm.) three times a day. In weak and debilitated patients this may produce slightly toxic effects, *e.g.*, soreness of the gums when the dose is reduced, these symptoms quickly disappear. Glycerite of bismuth has long been used as a tonic, and patients usually remark that they feel much better after taking this preparation. This form of bismuth should be administered for a period of three months, and after a brief rest for another 3 months in old standing cases. The advantage over injections is that the patient gets a continuous daily supply of bismuth, and not in large doses at frequent intervals.

Yaws or Framboesia. Yaws is a chronic disease of warm-climates caused by the *Spironema pertenue*. As regards causation and the general course of the disease, it closely resembles syphilis. As a result of its successful use in syphilis, bismuth has naturally been employed in the treatment of yaws. Extensive trials in British East Africa have shown that bismuth

compounds are nearly as efficacious as neo-salvarsan. Two or three injections of tartro-bismuthates in doses of 0.2 gm. in freshly prepared solutions at intervals of a week produce healing of the lesions, but it is probable that a larger number will be required to eradicate the parasites. Besides bismuthyl tartrates, bismuth subgallate (dermatol) has been used in 3 c.cm. doses of a 10 per cent. emulsion in oil given intramuscularly twice a week. Very good results were obtained with 10 injections, but this produced toxic effects. On a large scale patients have been treated with a single massive dose of dermatol; only 15 per cent. relapsed. Good results have been claimed with four weekly injections of bismuth subnitrate in 10 per cent. suspension in oil. Metallic bismuth has been used but this is more expensive. Bismutho-yatren A and Bismutho-yatren B have given good results; 2 to 17 injections on an average have to be given. The author has tried *bisnene* in doses of 0.1 to 0.15 gm. intravenously in a few cases with good results. The results are as good as those with neo-salvarsan and other bismuth preparations; it is much cheaper, more stable and costs less than a farthing a dose. Shircore (1926) treated 113,000 cases of yaws in secondary and tertiary stages with 6 injections of bismuth arsanilate given every other day; 75 per cent. were completely healed. Although bismuth preparations are admirably suited for mass treatment of this disease, recent work has shown that to eradicate the disease, a combined treatment should be carried out with bismuth and arsenicals till the serum reaction becomes negative.

Amoebic dysentery. Deeks (1908) first started treatment of dysentery with large doses of bismuth subnitrate by the mouth in Panama and found that it gave very promising results. In seven cases 180 gr. of the drug were given in effervescent form every three hours night and day; in chronic cases the dose is less but it is advisable to continue one or two daily doses for at least a month after convalescence is established. After the introduction of emetine, the treatment with bismuth subnitrate was supplemented by daily injections of emetine. James (1913) studied the effects of both bismuth and emetine on the vegetative forms of *E. histolytica* and found that the amoebæ passed by patients on emetine and bismuth treatments showed signs of degeneration but the changes produced differed with the two drugs. He suggested that bismuth subnitrate may be converted into bismuth sulphide in the gut and that in

this way it may deprive the amoebæ of hydrogen sulphide, which is possibly an essential element of their food supply. He advocated a course of 9 to 12 gr. of emetine by injections and 3 dr. of bismuth subnitrate suspended in water, by the mouth every 3 or 4 hours. Deeks (1914) thought that with the combined emetine and bismuth treatment every case of amoebic dysentery might be cured. James (1916) concluded that intestinal amoebiasis whether acute or chronic can be eradicated with liquid diet until the stools are formed, along with emetine injections carried to the point of physiological reaction and bismuth in not less than a teaspoonful dose 4 times a day carried over for a period of several weeks. York (1919) spoke very highly of the combined bismuth and emetine treatment and said that the treatment invariably cleared the stool of entamoebæ, a result which can by no means be achieved by emetine alone. James and Deeks (1924) gave an account of cases of amoebic dysentery treated with bismuth subnitrate alone in Panama, none of which relapsed. They believe that certain products of putrefaction are essential for the life of amoebæ, and that bismuth acts either by destroying the putrefactive bacteria, or by neutralising some products essential for the life of the amoebæ. Deuskar (1926) tried this treatment with excellent results in the Andamans. Knowles (1928) in a series of 55 cases found that the combined method failed to eradicate the infection from carriers, the proportion of probable cures to failures being 1:1.8 in his cases. He found that the treatment certainly improves results from the clinical point of view. James (1928) believes that the prolonged use of bismuth subnitrate in large doses, 12 to 14 gm. per dose, 3 to 5 times a day, combined with rest, irrigation of the gut when indicated and a proper diet, will give a high percentage of cures. He gives emetine according to the susceptibility of the patient to the drug. The patient is given a rigid, but nutritious diet and has to take bismuth for several months.

It will be seen from the above that combined treatment with emetine and bismuth is worthy of further trial. It is advisable to use bismuth carbonate instead of the subnitrate as the latter sometimes gives rise to nitrite poisoning due to absorption of the drug from the ulcerated areas.

Lupus erythematosus. This a chronic non-tuberculous affection of the skin characterised by disc-like patches on the surface with reddish edges and depression at the centre. The patch is covered with scabs which fall off gradually and leave a dull white cicatrix at the bottom. The etiology of the disease is unknown. Bismuth salts have been used in this condition with good results. Bismuth metal, bismuth hydroxide, bismuth oxychloride, or sodium bismuth thioglycollate suspended in oil is given intramuscularly once a week. The average dose ranges from 0.3 to 0.4 gm. Local treatment with mercury improves the condition in many cases.

MODES OF ADMINISTRATION

By the mouth. As already stated, only very minute quantities of bismuth are absorbed from the alimentary canal. The absorption is so slow and uncertain that this route of administration is not employed for the treatment of such diseases as syphilis. Tartro-bismuthates have been given orally but they are slowly absorbed and their effects are uncertain.

Subcutaneous and intramuscular injections. Subcutaneous injections of the soluble salts usually produce severe local reactions and, as they have no advantage over the intramuscular route, this route cannot be recommended.

Intramuscular injections of bismuth salts are said to be as effective therapeutically as intravenous injections. Bismuth therapy involves the same principle as intramuscular mercury therapy, *i.e.*, to establish intramuscular depots of slowly-soluble metal compounds, which may be gradually but continuously absorbed. The same difficulties are met with here, namely, that the absorption of the drug from these depots becomes progressively weaker till finally arrested by local fibrosis. The patient thus has a number of bismuth nodules in the body which do no good, but may do great harm if several of them suddenly break up or become otherwise activated.

'Trepol' and 'neo-trepol' are given intramuscularly with a thick needle in the superior gluteal region. Injections are given alternately on either side, not oftener than once a week as there is danger of cumulative poisoning. The injections are repeated until the Wassermann reaction becomes negative. Some authorities give 0.1 gm. at intervals of a fortnight. If symptoms of flatulence occur, especially in the morning, the interval between the doses should be increased.

Local reactions due to muscle irritation and necrosis may follow intramuscular injections. Pain and inflammation vary according to the nature of the compound used and the vehicle employed. The common type is a hard and painful swelling with considerable infiltration which may sometimes suppurate. The addition of 10 minims of a 2 per cent. butyn solution or phenol ($1/5$ gr.) to trepol reduces the pain effectively though

an area of tenderness may be left. Histological examinations five days after injection show varying degrees of necrosis of muscle cells and leucocytic infiltration. Watery solutions produce a more intense reaction than the oily solutions. Nodules in the tissues left after intramuscular injections of bismuth compounds are due to purely inflammatory reactions and are less likely to be produced when solutions are made in vegetable oils such as olive or almond oil.

Intravenous injection. The intravenous injections of soluble bismuth salts are so toxic that they cannot be recommended. The toxicity by this route is at least ten times greater than the intramuscular route.

As in the case of other heavy metals, agglutination and hæmolysis may occur after intravenous injections, with the formation of emboli. Even with such compounds as tartro-bismuthates, colloidal preparations or bismuth hydroxide, reactions may be produced immediately after injections. Cases of sudden death after intravenous injection of bismuth compounds with symptoms of colloidal shock have been reported. Kolmer (1926) is of opinion that the dangers of intravenous injection of tartro-bismuthates have been overrated, but he says that the intravenous route is not the method of choice, as absorption after intramuscular injection is fairly rapid. In acute cases of syphilis, when arsenicals cannot be given owing to hypersensitiveness, the intravenous route is preferable. Kolmer gives 0.01 gm. (1/6 gr.) of potassium tartro-bismuthate dissolved in 10 c.cm. of saline solution and sterilised by heating; no untoward effects are produced. Mercury is more toxic by the intravenous route than bismuth, the maximum tolerated dose of perchloride of mercury is 0.006 gm. per kilo., while that of the soluble tartro-bismuthates is 0.02 to 0.03 gm. Some authorities have shown that the danger of agglutination of erythrocytes is small, but bismuth may produce precipitation of serum-proteins in the same way as do the arsenicals or antimonials.

CHAPTER XXXIII

TOXIC EFFECTS OF BISMUTH

The toxicity of bismuth compounds has been worked out on animals. The earliest symptoms following intravenous injections of bismuth salts in experimental animals are loss of appetite, nausea, vomiting and diarrhoea; salivation and stomatitis with ulceration of the gums, tongue and buccal mucous membrane appear shortly afterwards. Weakness, slowness and inco-ordination of movements follow and tetanic convulsions may occur at intervals. The urine contains albumin and casts. The weakness gradually deepens into complete paralysis and the animals generally die. Post-mortem examination shows congestion and sometimes necrosis of the kidneys. Congestion and a black discolouration of the cæcum and upper part of the large intestine are also prominent features. The mucous membrane may show areas of patchy hæmorrhage, ulceration or necrosis. The histological changes produced in the kidneys and liver of rabbits, suffering from bismuth poisoning, following the administration of tartro-bismuthates, have been studied. These changes chiefly affect the convoluted tubules, the epithelium of which shows all kinds of degeneration ranging from severe cloudy swelling to extreme necrosis and calcification; the glomeruli are not affected. The lesions in the liver are not so marked; usually cloudy swelling of the cells, and fatty degeneration are met with; hæmorrhagic and necrotic foci may rarely occur. Following intramuscular injections in guinea-pigs, the changes produced in the liver and the kidneys are of a much milder nature than those produced by intravenous injections. Such experiments show, (1) that intramuscular injections are less toxic than intravenous injections and (2) that bismuth is most toxic for the kidneys, next for the liver and relatively non-toxic for the brain, heart, lungs, suprarenals and spleen.

Changes in human beings appear to be of the same nature, and symptoms are similar to those produced in animals. The toxicity of bismuth is comparatively low, undesirable effects are

comparatively few and generally not serious. In view of the extended use of bismuth in syphilis, these will be given in detail.

Symptoms. After intramuscular injection of tartro-bismuthates, the earliest symptoms observed are pain in the muscles and joints accompanied by loss of appetite and feelings of malaise and lassitude. These, as a rule, are not severe, but in exceptional cases intense pain in the larger bones, joints and groups of muscles, accompanied by rigors, fever, a feeling of compression in the chest and dyspnoea may occur a few hours (12 to 24 hours) after the injection. Rheumatoid pains of the ribs, spine and legs are characteristic; skin eruptions of the nature of erythrodermia or scarlatiniform erythema with purpura may occur. Jaundice is as a rule not met with and bismuth may be given to patients in whom arsenicals have produced jaundice. Local irritation at the site of intramuscular injection is not uncommon; a 'lead-line' may occur at the junction of the teeth and gums due to precipitation of bismuth sulphides; a blue line in the gums, odorous breath and bad taste in the mouth often precede it. Blue spots may appear under the tongue and in the mucous membrane of the cheeks; gingivitis is caused by the deposition of bismuth in the capillaries, producing partial blockage of vessels, congestion and loss of nutrition and formation of ulcers. Ptyalism is unusual and when present is not so severe as in the case of mercury. Bismuth is less likely to produce renal irritation than mercury, and albuminuria is therefore very uncommon even after 12 to 15 intramuscular injections of 0.1 to 0.2 gm. each of tartro-bismuthates. It is however advisable to examine the urine every week during the course of injections. Herxheimer's reaction, *i.e.*, pain and swelling of syphilitic lesions in the lymph glands, skin, etc., are sometimes seen after 2 or 3 intramuscular injections; vague pain in the heart and other parts of the body, which are probably due to provocative effects, sometimes occur. These effects however are not so common as with the arsenicals.

Toxic symptoms produced in human beings by the oral administration of bismuth subnitrate may be due, not to bismuth but to the nitrate portion which is reduced in the gut to nitrite and produces symptoms of nitrite poisoning. After a

large dose of this compound for radiography, methæmoglobinæmia, intense cyanosis, diarrhoea, dyspnoea and collapse may occur; death may even occur from paralysis of respiration. All these can be prevented by using bismuth subcarbonate instead. Considerable absorption of bismuth may however take place from wounds and raw surfaces and symptoms of acute or chronic poisoning may follow. Capillary thrombosis from precipitation of bismuth sulphide in the intestinal vessels has been known to occur.

Intramuscular injections and injections of bismuth compounds into long sinuses sometimes give rise to toxic phenomena, from excessive absorption of the metal. The condition of the patient is an important contributing factor. If the mouth and the gums are in bad condition there may be gingivitis, stomatitis, and halitosis (offensive breath); if the patient is a victim of gastro-intestinal disorders, he is more likely to suffer from diarrhoea and colic; focal infection of the teeth, tonsils and other tissues may predispose to dermatitis. Some individuals are naturally hypersensitive to bismuth. According to Kolmer, four factors are concerned in the production of toxic symptoms, (1) the drug, (2) the route of administration, (3) predisposing pathological state of individual patient and (4) hypersensitivity to bismuth.

The circulatory depression, that is noticed in animals receiving intravenous bismuth, does not occur after the clinical use of bismuth as an anti-syphilitic. Sometimes acute reactions due to colloidal shock may occur. The symptoms complained of are dizziness, pallor, rapid and weak pulse, dyspnoea, convulsions and collapse. Siderosis, halitosis, ptyalism, and gingivitis are commonly observed; various skin eruptions (purpuric, scarlatiniform, erythematous, urticarial, lichenoid, exfoliative dermatitis), renal irritation and provocative Herxheimer's reactions are sometimes seen. Stomatitis and gingivitis are the most troublesome symptoms.

The mechanism of production of siderosis, stomatitis, and allied lesions has been explained, but the muscle and bone pains are more difficult to interpret. These are probably due to a neuritis similar to that produced by arsenic and mercury.

Treatment of toxic reactions. In poisoning from large doses of bismuth compounds by the mouth, the stomach is washed out thoroughly and repeatedly and saline purgatives are administered. If bismuth paste has been given in a sinus it should be removed.

In case of acute poisoning due to a large accidental dose, the most dangerous lesion is tubular nephritis. If this is produced intravenous injections of sodium thiosulphate are indicated. As a rule muscular pains, malaise and anorexia disappear after a few injections, but if they persist and there is anæmia, loss of weight or ulceration of the gums, the treatment should be stopped. For gingivitis and stomatitis a mouth wash containing alum and potassium chlorate is the best. Ulceration of the gut is relieved by proper dietary and demulcents.

Cautions and contraindications. Before beginning a course of bismuth a thorough investigation must be made into the condition of the teeth, the liver function and the general health of the patient. If there is any such defect, refrain from giving the treatment till these have been attended to. Cleansing of the teeth and gums during the course is important; dietetic errors should be corrected to reduce the possibility of gastro-intestinal disturbances, such as diarrhoea and colic; the appearance of large quantities of albumin and casts in the urine also calls for suspension of treatment; if albumin had been present prior to treatment, soluble salts are better. The urine should always be examined before starting bismuth injections and during the course. In exceptional cases renal function tests may be necessary but liver function tests are not required. Sometimes a general asthenia with pallor and loss of weight occurs after bismuth injections, but this soon passes off. The drug has not yet been used long enough to warrant any definite opinion. We are only just beginning to find these out in the case of arsenicals and mercury compounds.

Mode of action of bismuth compounds. The mechanism by which bismuth compounds produce their spirochaeticidal action *in vitro* and *in vivo* is not clear. Tartro-bismuthates of sodium and potassium are capable of destroying the motility of *S. pallida* in very high dilutions,

and bring about their complete destruction when given by inoculations in rabbits. In both these respects mercuric chloride and mercuriochrome are more active than bismuth compounds. Levaditi believes that bismuth enters into a colloidal state and exerts a direct spirochaeticidal effect in this condition. The mechanism is probably similar to that of mercury and is largely dependent on the ease with which the bismuth ions are dissociated. There is no evidence to show that new compounds are formed by processes of oxidation or reduction, as is the case with organic arsenicals or antimonyl compounds. There is also no evidence to show that bismuth increases the production of spirochaeticidal antibodies by direct stimulation of the antibody-producing tissues. Kolmer (1926) stated that the concentration of bismuth attained in the blood after intramuscular injections is cumulative and is probably sufficient to kill spirochaetes. It is possible that the actual destruction of the parasites is due to the union of the metal with the proteins of the parasites.

It has been said that bismuth is activated by the body tissues into a hypothetical bismo-protein called *bismoxyl*. The power of tissues to transform bismuth into bismoxyl depends upon their glutathione content. It has been shown in the experimental syphilis of rabbits that bismoxyl cures syphilis not merely by stimulating the tissues and general immunity reactions, but by an actual destruction of treponemas. The therapeutic action of bismuth varies directly with the quantity of bismoxyl circulating in the body; this is termed the tissue-metallic potential. It would appear that the potential is higher when insoluble salts are used rather than metallic bismuth. Intravenous injections of bismuth compounds therefore seem to be inadvisable if this is correct.

Levaditi and Howard (1929) showed that when an extract of liver or suprarenal in saline is incubated at 37°C. with bismuthyl tartrates of sodium and potassium for three hours, and then flocculated at 70°C. for three hours, a precipitate is obtained. This precipitate, suspended in normal saline and injected intramuscularly in rabbits, cured them of syphilis in doses of 0.00125 gm. of metallic bismuth per kilo. body weight and even doses of 0.000312 gm. cured after some time. They suggested that minute quantities of metallo-proteins act synergetically with the immune bodies of the tissues.

PREPARATIONS OF BISMUTH

During the last five years a large number of new compounds, chiefly organic have been introduced for intramuscular and also for intravenous injections. Many of these are still in the experimental stage. While as a general rule those having the highest percentage of the element are the most effective, it must be borne in mind that the form in which bismuth exists and the manner in which it is

combined have much to do with the efficacy of the product. The ease and rapidity with which bismuth ions are dissociated in the body, as has been already pointed out, are important factors in their therapeutic action. In order to form a clear conception of the nature of action of these compounds, it will be advantageous to consider the physical and chemical properties of bismuth. Bismuth is situated close to arsenic and antimony in the periodic system of elements. Like arsenic and antimony, bismuth is an amphoteric element and therefore yields cation (electropositive bismuth) and anion (electronegative bismuth) compounds. The majority of bismuth compounds in current use are electropositive or cationic. The bismuth content of these products varies from about 20 to 80 per cent. These preparations can be grouped into four general classes:—(1) insoluble, suspended in aqueous medium, such as the metal in dextrose solution; (2) insoluble, suspended in oil, such as bismuth salicylate in oil; (3) soluble, suspended in oil, such as potassium bismuth tartrate; (4) soluble, dissolved in aqueous medium, such as bismuth sodium tartrate in sucrose solution or water.

The products containing electronegative or anionic bismuth have come into use more recently. They are represented by two general types:—(1) soluble haloid bismuthites with about 21 per cent. of bismuth, *e.g.*, sodium iodo-bismuthite in ethylene glycol; and (2) sodium bismuthate with about 73 per cent. of bismuth. Electronegative bismuth compounds are claimed to possess several advantages over the electropositive compounds though both series of compounds are in common use. Electronegative bismuth penetrates the cerebral tissues better and therefore is to be preferred in neurosyphilis. These compounds are better absorbed and have a much lower toxicity than the cationic products. Most of the compounds at present known are toxic, but further research will probably give us compounds which are more parasitotropic and less organotropic.

A number of preparations of bismuth have been introduced recently for the treatment of syphilis. Those generally used are:—

I. Preparations containing metallic bismuth.

Metallic bismuth 0.2 gm. in 1 c.cm. of 5 per cent. glucose solution is sold in ampoules for intramuscular injections. Dose 0.5 to 1 c.cm. **Bismotab** is a preparation of 20 per cent. bismuth in 5 per cent. glucose solution; dose 0.5 to 1.0 c.cm. **Neo-trepol** is a 10 per cent. suspension in sterile isotonic saline solution. Dose 1.5 to 2.0 c.cm. intramuscularly every week. **Bismuthyl** is a 10 per cent. suspension in glucose medium. Dose 2 c.cm. every 5 days until 12 to 15 doses.

Metallic bismuth preparations are preferred to others on account of their being non-toxic; their absorption rate is uniform and the action is steady. They are specially useful in syphilitic affections of the heart and the nervous system. Care should be taken during intramuscular injection that none of the drug gets into the blood stream, as

this may cause paralysis and death in two hours. Metallic bismuth can also be given by deep subcutaneous injections.

Colloidal bismuth has been given intramuscularly as well as intravenously. Experiments on rabbits, guinea-pigs and dogs show that it can be given in high concentrations. The toxic dose for the guinea-pig is 0.095 to 0.35 gm. per kilo.; concentrations up to 4 per cent. do not produce shock, embolism or death. Signs of toxic action are tremors, convulsions, congestion and hæmorrhage in the kidneys, liver and intestines.

II. Inorganic preparations of bismuth.

Bismuth hydroxide suspended in, (1) water and glycerine, (2) in sterile oil, containing minute traces of mesothorium bromide.

Muthanol is a suspension of the radio-active oxide in oil; it is sold in ampoules of 2 c.cm. containing 0.15 gm. of bismuth oxide.

Casbis is a sterile oily suspension of activated hydrate of bismuth. In consequence of the very fine state of subdivision, it is remarkably free from causing any irritation when injected. It is slowly absorbed and produces a continuous and well-sustained effect. The dosage, to begin with, is 0.5 c.cm., followed by 1 c.cm. at an interval of 3 days—a total of about 15 to 20 c.cm. being necessary. Children should have a starting dose of 0.05 c.cm., followed by 0.1 to 0.2 c.cm., to a total of 1.5 to 2 c.cm.

Bismol is an oily suspension of bismuth containing 0.15 gm. of bismuth hydroxide in 2 c.cm. of oil. It is said to be satisfactory in florid types of syphilis. **Sodium bismuth iodide** (sodium iodo-bismuthite) in ethylene glycol containing 0.1 per cent. acetic acid, each c.cm. containing the equivalent of 0.012 gm. bismuth. This preparation has been introduced by Hanzlik and his co-workers. It is well-tolerated locally and internally and is fairly rapidly absorbed and excreted; and as it appears in the cerebrospinal fluid, it seems worthy of trial as a preventive of neurosyphilis or for its early treatment.

Bismuth oxychloride. Lomholt recommends the use of a watery preparation (suspension) of bismuth oxychloride (bisoxyl), so prepared that the particles have a diameter of from 3μ to 4μ . He considers that this preparation is sufficiently non-irritant and gives a correct rate of absorption of the metal.

III. Organic preparations.

Alkaline bismuthyl tartrates. These compounds can be divided into two classes.

(i) *Neutral compounds known as Bismuthyl tartrates or Carbo-bismuthates* which are either soluble or insoluble. They are prepared by dissolving bismuth oxy-tartrate in alkali, the alkali bismuthyl tartrate being obtained as a powder by evaporation or precipitation with alcohol. They are used for injection against protozoal disease. The

neutral compounds for injection are sodium tartro-bismuthate, potassium tartro-bismuthate and sodium potassium tartro-bismuthate.

(ii) *Acid preparations*, frequently described as "bismuth tartrate soluble." They are obtained by treating bismuth hydroxide with a solution of the alkali acid tartrate.

A number of proprietary preparations similar in composition has been put on the market under various trade names; **Trepol** is tartro-bismuthate of sodium and potassium. Dose 3 gr. (0.2 gm.) intramuscularly every week till 2 to 3 gm. are given. This compound is also given in 10 per cent. suspension in sterile oil. Ampoules or sterules containing 3 gr. (0.2 gm.) in 30 minims (2 c.cm.) of water are sold under the name of **Bismutol**. **Luatol** is a tartrated bismuth preparation; dose 1 c.cm. of the aqueous solution containing 0.1 gm. of the compound. A course consists of 10 to 20 c.cm. given in weekly injections of 1 to 2 c.cm. **Bismoluol** is a dipotassium bismuth preparation. A suspension of potassium bismuthyl tartrate in a medium containing sulphur has been used.

Bismuth salicylate is a white powder insoluble in water, alcohol and glycerine which has been used for intramuscular injections. **Bis-antol** has been introduced by May & Baker, Ltd. It is a 10 per cent. solution of bismuth salicylate in neutral vegetable oil, 1 c.cm. of the suspension containing 0.057 gm. of metallic bismuth. The injections are said to be painless. The course of treatment comprises 12 to 15 injections of 1 c.cm. of the suspension, given intramuscularly at intervals of 3 to 5 days. **Sodium bismuth thioglycollate** is a water-soluble preparation. **Thiobismol** is a similar preparation containing 37.5 per cent. of metallic bismuth. It is said to be non-irritating and to influence the disappearance of the spirochaetes more favourably than insoluble bismuth preparations. The dose for each injection is 0.2 gm. of the powder, given intramuscularly dissolved in 1 c.cm. of distilled water. **Bismuthyl gluconic acid** and the sodium salt of bismuthyl saccharic acid have been used in 10 per cent. watery solutions. **Bismuth camphor carboxylate** (**Bismocymol**) is a white powder with a camphoraceous odour. A suspension in oil is used, 1.0 c.cm. containing 0.05 gm. of bismuth. Kolmer states that it produces less local reaction than insoluble bismuth compounds and that it has proved of great value in the treatment of children and also adults who do not usually tolerate intramuscular injections. Constitutional reactions and signs of renal irritation have not been observed. **Bismogenol** is a compound of bismuth and hydroxybenzoic acid and **Mitamel** which is said to be a compound of bismuth and trichlorobutylmalonic acid are German preparations.

Chopra and his collaborators have introduced an organic aromatic compound of bismuth known as **Bisenene**. This compound is practically the bismuth analogue of urea-stibamine and therefore is the sodium salt of para-amino-phenyl-bismic acid in combination with urea. It

contains 50.1 per cent. of bismuth and has a low toxicity, its M.L.D. being 500 mgm. per kilo. in white mice. This compound can be given intravenously without producing toxic symptoms. Its value in syphilis has not been determined but is quite effective in the treatment of yaws. It is possible that this series of aromatic compounds may have some potent therapeutic properties.

IV. Alkaloidal iodo-bismuthates. A number of these compounds were prepared of which iodobismuthate of quinine or **Quinby** is commonly used. **Biquinyl** is a commercial preparation of iodo-bismuthate of quinine and bismuth oxychloride.

V. Liposoluble bismuth compounds. Various bismuth compounds soluble in lipoids have been prepared, instead of suspensions of bismuth. **Embial** (540 D Merck), **Blazan** (methyl-hydrocinnamate) are such compounds; **Spirobismol** is a double iodide of quinine and bismuth associated with lecithin. It is said to be specially suitable for syphilis during pregnancy. **Bismuth camphor carboxylate** (Cardyl) and basic Bismuth α -carboxylethyl- β -methyl-nonoate (**Bivatol**) have been studied. The chemotherapeutic index of the latter compound is 1:33 for rabbit syphilis, and it is rapidly absorbed. Not only do the primary lesions rapidly heal, but the infection is totally eradicated as the animal becomes susceptible to infection with *S. pallida* again. The action of **Bivatol** has been favourably reported on by several workers both in England and in Europe. It is available as a neutral limpid oily solution containing 40 mgm. of bismuth metal per c.cm. The dose is 2 c.cm. of the suspension given intramuscularly twice a week—a course comprising 12 injections. Levaditi regards it as the treatment of choice in syphilis. The fact that it is a solution and not a suspension ensures exact dosage, while the slow rate of absorption avoids shock and toxic disturbances. Schwartz speaks very highly of this liposoluble compound, which he has used in all stages of syphilis with most favourable results. **Bileposol** is similar in composition to bivatol. It contains 0.04 gm. of bismuth per c.cm. of the suspension and is given in doses of 2 c.cm. twice weekly. Its rate of excretion is very slow and may continue for as long as one and a half to two months after cessation of treatment.

VI. Compounds of bismuth and organic arsenicals. It is generally recognised that combined treatment with bismuth and arsenic is more effective than either drug alone. Efforts have therefore been made to present a compound of bismuth and arsenic in such a form as to get the therapeutic effects of both drugs simultaneously. **Bismarsen** or bismuth arspenamine sulphionate is the sodium salt of a bismuth derivative of arsenobenzene methylene sulphonic acid with inorganic salts. This is an American product and contains approximately 15 per cent. of arsenic and 23.25 per cent. of bismuth. It is given intramuscularly twice weekly, in doses of 0.2 gm. dissolved in

1 c.cm. of distilled water to which 2 min. of 2 per cent. butyn is added, the full course being 24 to 32 injections. Its spirochaetocidal effect is considered by some to be slower than that of the arsenical compounds and its healing effects not so marked. In early syphilis this compound was very effective, toxic effects were few, and there was a definite tonic effect. In neurosyphilis it has no effect, though it is said to relieve the lightning pains of tabes; it had no effect on optic atrophy. The drug is well borne by children. Levaditi (1926) described bismuth stovarsol or **Bistovol** which is basic acetyl-amino-oxyphenyl-arsenate of bismuth which did not prove very effective against syphilis. He has also prepared soluble **Bistovol** (H13) which is p-hydroxy-m-acetyl-amino-phenyl arsenic acid, bismuth salt of p-amino-phenyl arsenic acid and bismuth tryarsamide-n-phenyl glycinamide-4-arsenic acid. The first has a well-marked antisyphilitic action, having a therapeutic index of 1.35 in syphilis in rabbits. It can be given in 2 per cent. solution intramuscularly, is quite painless and produces rapid healing of primary and secondary lesions. It can be given by the mouth in solid form or as 10 per cent solution and was tolerated in 2.0 gm. doses daily for 8 to 11 days. Even with this high dosage no toxic symptoms were produced and lesions healed; serological reactions improved. **Bismuth arsanilate** is given as a suspension in oil intramuscularly and has a therapeutic efficiency equal to that of bistovol. Bismuth tryarsamide contains 40.5 per cent. bismuth and 14.5 per cent. arsenic. This preparation was tested by Levaditi (1928) in natural spirochaetosis of the rabbit (*S. cuniculi*). The spirochaetes disappeared on the second day after intramuscular injection of 0.1 gm. per kilo. Its curative action is somewhat slower than that of bistovol or bismuth arsanilate.

Bismutho-yatren is said to be an aqueous solution of sodium bismuth-iodohydroxy quinoline sulphonate, containing 10 mgm. of metallic bismuth per c.cm. **Bismuth-yatren B** is a quinine derivative and contains 36 mgm. of metal per c.cm.

Mesural contains mercury and 1½ gr. (0.11 gm.) of bismuth in each c.cm. It is given by deep intramuscular injections, 0.5 c.cm. being the first dose in an adult, increased to 1.0 c.cm. Eight to twelve injections giving a total of 14 to 20 gr. (1.0 to 1.3 gm.) constitute a course.

Quinine-iodo-bismuthate occurs in the French Codex Supp. 1929; dose 0.15 gm. usually given suspended in olive oil. **Bi-quinyl** is a double iodide of quinine and bismuth; ampoules containing 0.3 gm. in 3 c.cm. of oil are on the market. These preparations were introduced with the idea that the combination of quinine and iodine with bismuth will enhance the spirochaetocidal action.

*Bismuth Preparations for Injection in Syphilis**(Modified from Harrison)*

Chemical compound	Medium	Trade names	Content of bismuth in per cent. of the dried compound
*Bismuth metal	Isotonic saline Creo-camphor base.	Neo-trepol Bicreol	96
*Bismuth hydroxide	Glucose solution	Bismuthyl	97
	Oil	Muthanol	64
	Oil	Curalues	86
	Oil	Bismol	
*Bismuth oxychloride	Water	Spirillan	
	Camphor water	Biscolorol	80
	Chloretone sol.	Bisoxyl	
Tartro-bismuthate of sodium and potassium (T.B.S.P.)	Oil	Bismutol	50
	Water	Luatol	32
	Water or oil	Tarbisol	57
	Soluble powder	Bi 86	86
	Sulphur water	Sigmuth	25
Iodo bismuthate of quinine	Oil	Quinby	24
	Oil	Rubyl	19
	Oil	Vijochin	20
	Oil	Bismogenol	
Basic salicylate of bismuth	Oil	Bi-quinil	50
Iodo-bismuthate of quinine and bismuth oxychloride			
Iodo-bismuthate of vanadium	Oil	Neoby	20
Ethylene diamino bismuth gallate	Water	Galismuth	1 c.cm. = 0.8 Bi
Colloidal bismuth		Bismuthoidal	...
Trichlorbutyl malonate of bismuth		Milanol	...
*Bismuth camphor carboxylate		Bismocymol	...
Basic carbonate of bismuth	Oil	Trepol	..
Bismutho-tartrate of potassium	Oil	Nadisan	.
Sodium-bismuth derivative of trioxybenzoic acid	.	Benzo Bi	20
Oleate of bismuth	Oil	Oleoby	20
Subgallate of bismuth	Oil	Dermatol	50
Amalgam of Bi and Hg	Oil	Bisermol	75

*Preparations commonly used

CHAPTER XXXIV

MERCURY AND ITS DERIVATIVES

Mercury was the first drug to be used as a specific disinfectant for the body tissues, for it was employed in Europe in the treatment of syphilis as early as 1500 A.D., and until the discovery of arsphenamine in 1905 it remained the only effective remedy against this disease. Its importance as a therapeutic agent in syphilis has suffered a set-back of late years as it has been replaced by bismuth. Mercurials have however a powerful destructive action on some of the pathogenic protozoa and a number of new mercury compounds have been introduced in medicine during recent years. Renewed interest has therefore been created in the subject, and it has been thought necessary to discuss these in some detail.

PHARMACOLOGICAL ACTION

External action. Mercury has a powerful toxic action on all protoplasm and mercurial compounds for this reason are active germicides. This germicidal effect depends chiefly on the concentration of mercuric ions in their solution, and on the precipitation of proteins. Absence of protein precipitation is important because it diminishes local irritation, favours the penetration of the mercury and obviates the absorption of the mercury ions by the precipitates.

A large number of mercury compounds are used externally for their antiseptic and germicidal properties. Sollmann has classified them according to the degree of their ionization, as this seems to be the most important factor which governs their bactericidal action.

Class I. Simple highly-ionizable inorganic mercuric salts. Mercuric chloride is one of the important members of this group. It is a most powerful antiseptic and inhibits the growth of many micro-organisms in as low a dilution as 1 in 300,000. Non-spore-bearing bacteria are killed in dilutions of 1 in 20,000 but anthrax bacilli are killed only in 1 in 1,000 concentration. Tubercle bacilli are rather resistant. *In vitro*, *Treponema pallida* are killed in dilutions of 1 in 200,000. Mercury has a stronger affinity for spirochaetes and the related group of organisms, but it has little effect on the parasites of malaria and sleeping sickness. Its practical utility however is limited, on account of its poor penetration due to the precipitation of proteins and its toxicity. It is used as

an antiseptic lotion for sterilising the hands, in a strength of 1 in 1,000. As the solutions are irritant to mucous membranes and have a corrosive action, they should be used with caution. One in 20,000 to 1 in 10,000 is quite effective and if stronger concentrations are used, inflammation of the mucous membrane and serous surfaces may be produced. The coagulation of the proteins gives a peculiar ashy corroded appearance to the mucous membrane. The tissues underneath present a reddened appearance and prolonged contact may lead to necrosis.

Class II. Moderately ionizable mercuric compounds. Potassium mercuric iodide is a typical example. This compound is obtained by dissolving mercuric iodide in a slight excess of potassium iodide. The antiseptic activity of this compound is practically the same as that of mercuric chloride, but the local irritant effect is much less. It tends also to get precipitated in contact with the tissues on account of the rapid diffusion of the alkaline iodide.

Class III. Poorly ionizable mercuric compounds. Mercuric oxycyanide, cyanide and benzoate, produce very little irritation of the mucous membranes and unlike other salts can be used for their antiseptic effect on sensitive surfaces such as the conjunctiva, and urethra. Several organic compounds belonging to this class have been prepared, *e.g.*, novasurol, meroxyl, mercurosol, afridol, metaphen. These have largely displaced the oxycyanide and cyanide compounds. Meroxyl may be used in concentrations ranging from 1 in 1,000 to 1 in 200 and merbaphen in concentrations of 1 in 10,000 to 1 in 1,000. Novasurol and salyrgan are not used as external antiseptics.

Class IV. Mercuric fluoresceins. These compounds were first introduced in 1919 and are characterised by their non-irritant properties when applied to the skin and mucous membranes. Mercurochrome 220 soluble is the most important member of this group. Flumerin (sodium hydroxy-mercuri-fluorescein) is also sometimes used, though it is recommended intravenously for syphilis.

Mercurochrome is now considered to be a highly efficient non-irritant antiseptic and is being widely used. A 2 per cent. solution causes only slight and brief irritation of sensitive mucous membranes, *e.g.*, the urethra. It is used especially in genito-urinary practice but has not received much popularity as an antiseptic for the skin and the mucous membrane of the mouth, throat, etc., as it cannot penetrate the tissues to any great extent and only acts on the surface bacteria and is ineffective against the spore-bearing organisms. It will be dealt with at length later.

Class V. Water-insoluble mercurials. These do not produce any immediate effects, but since they are gradually dissolved by the proteins and salts of the tissues they develop some local irritation and antiseptic action. Yellow mercuric oxide and ammoniated mercury are commonly used in ophthalmology and dermatological practice. Calomel

has also been used as a dusting powder for sluggish ulcers, ulceration of the cornea, etc. A 33 per cent. ointment is employed as a prophylactic against syphilis. A mild mercurial ointment which contains 30 per cent. of finely divided metallic mercury is used for destruction of lice.

Nature of the bactericidal action of mercury. The nature of the bactericidal action of the different mercury compounds is difficult to explain. The differences in the degree of solubility and ionization of the various salts and compounds are no doubt very important factors as has been rightly stressed by Sollmann. There are however certain factors which cannot be satisfactorily explained. Thus for example, salts like mercuric nitrate and mercuric acetate are much less powerful antiseptics and have a much less disinfectant action than mercuric chloride, though the above salts are equally freely dissociable. The peculiarities in the action of mercury externally are probably due to its action being dependent upon absorption. This causes mercury to act upon bacteria in high dilutions, but a certain time is necessary for absorption to occur, and any other substance that absorbs mercury will prevent it from acting upon the bacteria. The mere absorption of mercury upon bacteria does not kill them, but sufficient time has to be allowed for the mercury to penetrate into the organism before death occurs.

Internal Action. The internal action of mercury compounds, specially those in organic combination, will depend upon their solubility and diffusibility. The organic compounds are probably broken down into simpler substances in the tissues, the dissociation occurring in successive stages, and the intermediate compounds, whatever their structure may be, will possess probably the same pharmacological action as that exhibited by the original compound.

Respiration. The respiration is accelerated and deepened with moderate doses of mercury, probably due to stimulation of the medulla; large doses paralyse respiration; 2 to 4 mgm. of mercury per kilo. brings about these changes in respiration and circulation in the animals and 6 mgm. per kilo. may be regarded as the average dose necessary to cause paralysis of respiration.

Circulation. Blood pressure. Intravenous injections of soluble inorganic salts of mercury in animals such as dogs, cats and rabbits produce an abrupt, marked and persistent fall of blood pressure, there may be an initial rise of pressure in some cases. The changes in the blood pressure produced by injection of the organic mercury compounds are milder. Jackson (1926) using organic mercury compounds found that about 3 c.cm. of a 2 per cent. solution caused an elevation of pressure instead of a fall, the rise being most marked with 'salyrgan'. Subsequent injections produce smaller rises of pressure till a fall replaces the rise produced by the early injections.

Heart. The action of small amounts of mercury upon the heart was first studied by Dreser (1893) who found that as little as 3.8 mgm. of mercury potassium thiocyanate in 40 to 50 c.cm. of defibrinated ox blood resulted in paralysis of the perfused frog's heart, but that equal or larger quantities of mercury hyposulphate had no effect. The inorganic salts and so also the organic compounds, such as mercurochrome, rapidly produce cardiac irregularities and fibrillation.

The response of the isolated heart to the action of mercury varies in different animals. The frog's heart is very resistant to the action of mercury and a concentration as high as 1 in 50,000 is necessary to show any marked effect. The turtle's heart responds in as low a concentration as 1 in 1,000,000. In all cases mercury produces depression, irregularity and delirium cordis.

McCrea and Meek (1929) studied the effect of small amounts of mercuric salts upon the automatic and conduction mechanism of the heart. They found that various irregularities of the conduction mechanism occur after intravenous administration. At first there is stimulation of the sino-auricular node attended by an increase in the rate of the heart beat. Later, depression sets in with diminution in the automaticity and susceptibility of the conducting tissue from the sino-auricular node downwards, till fibrillation or paralysis supervenes. Recent work has however shown that the mercury ion in a high state of dilution has a definite stimulant action on animal tissues. A 1 in 1,000,000 concentration of mercuric chloride added to the perfusate distinctly stimulated the isolated mammalian heart and increased its force of contractions.

Gastro-intestinal tract. Mercury, by whichever route it is administered, exercises a selective action on the gastro-intestinal tract and increases the normal peristaltic movements. When soluble salts are administered orally, the effects on the mucous membrane are very severe. Hyperæmia, redness and swelling are immediately produced which commonly end in ulceration of the mucous membrane. The symptoms associated with such lesions are generally diarrhoea with rice water stools, intense pain, tenesmus and passage of blood and mucus with the stool. The insoluble salts like calomel dissolve so slowly and to so limited a degree that the irritative phenomena observed with the soluble salts are not manifested but catharsis is produced. Calomel is widely employed for this purpose and it produces a soft stool without pain or griping.

Mercury has very little action on the ferments of digestion. Large doses may precipitate pepsin. The antiseptic action on the intestine, especially of calomel, is due to retardation of putrefaction and decomposition of foodstuffs by increased peristalsis that hurries the contents down the intestinal canal.

Kidney. The kidneys are stimulated with small doses and diuresis is produced. The mechanism of mercurial diuresis has been explained

on the basis of a mild renal irritation, which favours filtration through the glomeruli and probably hinders reabsorption in the tubules. That there is definite renal stimulation has been proved by the experiments of Gœdert (1928) who transplanted the kidneys in novasurol-treated dogs and found that the novasurol-kidney excreted much more urine than the normal kidney. The diuretic effect of the organic mercurials will be discussed later.

Large doses of mercury produce characteristic changes in the kidney in a few hours with consequent anuria, cloudy swelling and necrosis of the epithelium of the tubules. The congestion of the glomeruli and the necrosis of the tubules form the prominent features in post-mortem appearances; the latter may be filled with necrosed cells on which are deposited lime salts and phosphate. The changes are more marked with soluble preparations like the perchloride of mercury than with the insoluble ones.

Central nervous system. The action on the central nervous system is not marked in therapeutic doses. Tremors and giddiness may be temporarily produced. Workers in mercury mines, in mirror works, barometer and thermometer factories are specially liable to develop poisoning symptoms from absorption of mercury. These symptoms consist in great muscular weakness which may develop into hallucination and delirium. Another feature of the nervous affections is a peculiar tremor which involves the hands and arms, and ultimately the legs. Shooting pains along the course of the nerves and joint pains have also been observed. The higher centres of the brain are rarely affected by mercury. In chronic poisoning, signs of hallucination and delusion may point to an affection of the cerebrum but they are extremely rare.

Metabolism. The effects of mercury on metabolism are not fully understood, but in general resemble those of arsenic and phosphorus. Small doses are said to improve the nutrition and lead to acceleration of metabolism of proteins. Prolonged administration may give rise to cachexia. The red blood corpuscles and hæmoglobin content are increased in healthy individuals; in syphilitics there is an initial lowering of the hæmoglobin percentage which is later on considerably increased. In acute poisoning there is glycosuria and disappearance of glycogen from the liver. The effect on the body temperature is negligible.

Fate in the body. Metallic mercury and mercury compounds are readily absorbed from all surfaces including the intact skin. Complex chemical changes are said to occur in the course of absorption. Mercurous compounds and metallic mercury are oxidised and the mercuric salts form soluble compounds with proteins, sodium chloride and alkalies. The absorbed mercury remains in the blood only for a short time but may remain in the tissues for a very long period and continue to exert its specific action by slow ionization and reabsorption.

Excretion. The excretion of this metal takes place mainly through the urine and faeces. Traces are also found in the bile, sweat and saliva; it is not excreted in milk. The form in which it is excreted in the urine is not known.

The rate of excretion varies greatly with the nature of the mercury compound, the method of administration and the diet. The rate of excretion of the water soluble compounds are different from the water-insoluble compounds. Thus with mercury salicylate which is insoluble in water, the excretion gradually increases up to the ninth day, while with a soluble compound the highest rate of excretion is reached on the fourth day. Hence soluble compounds should be given therapeutically in repeated small doses, the total quantity being necessarily smaller than in the case of insoluble ones. Certain insoluble compounds such as yellow mercurous iodide though insoluble probably become water-soluble before being absorbed and this may explain the variability of excretion that may be seen with different insoluble compounds. In addition diet may be an important factor in determining the absorption and excretion of mercury. Under ordinary balanced diet, the daily excretion of mercury in the faeces is much lower than in the urine. But the addition of acid substances greatly augments the rate of faecal excretion. Cole and others (1926) showed that by adding acids to the dietary the faecal excretion of mercury can be increased tenfold, while the urinary excretion is increased only three and a half times.

In general, it may be said that with therapeutic doses excretion declines rapidly and becomes insignificant within a week after the administration ceases. In the case of metallic mercury and colloidal mercury injections, absorption depots are maintained and traces may be excreted intermittently for as long as six months or even longer. A considerable portion of the absorbed mercury however is retained indefinitely in the tissues.

The excretion has been studied clinically by a number of workers and the figures agree in their general features. As the course of urinary excretion is a good indication of the absorption of the metal into the tissues and its mobilisation for therapeutic action, it will be interesting to see how this factor varies with the different mercury compounds in common use. Sollmann's summary of the course of urinary excretion is particularly instructive. He has grouped them into three different types:

1. The completely periodic and remittent type of excretion is met with in all intravenous injections, organic, ionizable, and colloid suspensions. The excretion rises and declines acutely, reaching its maximum in one to two hours, and ceasing practically in 8 to 24 hours. This type applies also to the intramuscular injection of several non-precipitating organic compounds (novasurol, flumerin, saliyrigan).

2. The incompletely remittent cumulative excretion is illustrated by the salicylate suspended in oil. The excretion rises and declines rapidly as in the periodic type, but the decline is quite incomplete so that the excretion of the successive injections becomes superimposed, cumulative and even somewhat potentiated.

3. The continuous progressive excretion is obtained when the absorption is nearly continuous so that there is no opportunity for remission. This occurs when depots are established by inunction, and by intramuscular injection of sparingly soluble preparations (gray oil or calomel). The excretion in the after period declines slowly, so that the therapeutic level is maintained for a week or two after the end of the course. Transitions between types (2) and (3) are furnished by oral administration, and by daily intramuscular injections of ionizable compounds, *e.g.*, sodium mercuric iodide.

The fate of absorbed mercury and its distribution in the body tissues is not fully known. Its concentration in the blood, as has already been pointed out, declines rapidly and only minute traces can be detected in it afterwards. Its concentration in the urine approximates to that in the blood. The kidneys usually contain the highest concentration and the largest amount. The liver comes next in order; in cases of intravenous injections of colloidal solutions and dyes, the concentration of the metal in this organ is especially high. The spleen, brains and lungs come next in order. The fat and the muscles contain a low concentration, but the quantity as a whole in the latter is fairly high. Mercury is found in the bones and has been detected by Kolmer in necrotic bone and in the wall of an aortic aneurysm. In the body fluids and in the amniotic fluid mercury is found in fairly good concentrations. It passes through the placental circulation and hence it is claimed that congenital syphilis may be treated by mercurial inunction of the mother. Mercury has been demonstrated quantitatively in the cerebrospinal fluid. Probably mercury is present in this fluid as a freely soluble compound and is present there as a diffusate from the blood. The concentration of mercury in the spinal fluid increases in direct proportion to the number of doses, and the amount of the drug administered.

It has already been pointed out that during the period of active excretion the mercury content of the tissues is high, but after that period there is a drop in the excretion rate; bones and to a lesser extent the liver may act as reservoirs for the unexcreted mercury. This phenomenon is influenced by the pH of the blood and the tissues. Obviously prolonged administration of mercury, especially if the diet is alkaline, results in the deposit in the body of large amounts of mercury which may be released suddenly from the depots by any reaction that lowers the pH of the blood or tissues. This is one of the potential sources of mercury intoxication that have been noticed in subacute or delayed poisoning.

CHAPTER XXXV

THERAPEUTIC USES OF MERCURY

As an antiseptic. Soluble salts of mercury, as has been already stated, are used as skin and local antiseptics. Perchloride of mercury (1 in 1,000) solution is the commonest antiseptic used in surgical theatres and emergency operation rooms. Mercury oxycyanide in 0.2 to 0.6 per cent. solutions have been used as a lotion for wounds. Similarly gauze for surgical dressings has been impregnated with mercurio-zinc cyanide.

As cathartic and intestinal antiseptic. Perchloride of mercury is seldom used internally as it is a strong irritant and corrosive and may give rise to toxic symptoms if the dosage is not properly controlled. In small doses however it is still used by clinicians for its antiseptic and astringent effects on the gastro-intestinal tract. Insoluble mercury salts are however preferred for this purpose. Calomel dissolves so slowly and to so limited a degree that the intestinal irritation and toxic symptoms, commonly produced by the soluble compounds, are not manifested at all. On the other hand, a very mild irritation is produced which stimulates both the large and the small intestines and increases their peristaltic movements, resulting in catharsis. Ordinarily, calomel produces dark-green semi-solid stools in ten to twelve hours. The green colour is due to biliverdin. The appearance of biliverdin in the stools has been considered to be due to the effect of calomel causing an increased flow of bile. This however is an erroneous idea. Numerous investigations with biliary fistulæ have shown that calomel does not increase the flow of bile.

Calomel is commonly used in therapeutics for its antiseptic action and it is one of the most useful and efficient antiseptics known. The antiseptic action is said to be due to the slow formation of mercuric chloride from calomel in the alkaline medium of the pancreatic juice. Following the administration of calomel, the bacterial flora is definitely diminished and this

is reflected in the decrease of the urinary indoxyl. Large doses of calomel may favour bacterial growth by diminishing intestinal resistance.

Calomel is administered either in a single dose of 1 to 5 gr. or more commonly in divided doses of $\frac{1}{4}$ gr. every hour until 2 to 3 gr. are given. The method of giving the drug in divided doses is more favoured, in view of the fact that this method ensures better solution and consequently more efficient action. Grey powder (hydrarg. cum creta) is specially suited for children. The mercurials are of value in obstinate constipation attended with biliousness and they can be conveniently administered at night followed by a saline purgative in the morning.

Calomel should not be used continuously for a long time on account of its systemic actions. This is ordinarily unimportant because any excess is generally excreted before it is absorbed. But conditions in the gastro-intestinal tract, *e.g.*, irritations, ulcerations, may favour rapid absorption and toxic symptoms. It is therefore always advisable to follow calomel after 6 hours by a saline purgative.

As a remedial agent in syphilis. The most important therapeutic use of mercury is in the treatment of syphilis. It is the classical remedy and has been in use from the time when syphilis was first recognised (1495). Until the discovery of arsphenamine in 1905, mercury held a place above all other remedies. With the knowledge of the antisiphilitic properties of arsenic and bismuth, mercury has fallen into the background and little attention has been paid to it in recent years though it is still used as an adjunct to arsphenamine treatment.

Effects of mercury in syphilis. Mercury is directly fatal to the treponema *in vitro*, and is effective in the local prophylactic treatment. With therapeutic doses however the concentration of mercury in the blood is far too low to be actively parasitocidal. If sufficiently prolonged treatment is carried on with mercury alone, permanent cure may be obtained. This has been proved by Kolle in experimental syphilis of the rabbit but it is not safe to rely upon it clinically.

The action of mercury in syphilis is similar in nature to arsphenamine and bismuth but it is distinctly slow and progressive. The number of treponemas in the primary lesions is greatly diminished after the administration of mercury. The superficial secondary lesions, *e.g.*, eruptions, mucous patches, clear up in the majority of cases. The tertiary lesions are checked and arrested but may not disappear completely. If treatment is stopped too early the disease again becomes active and more resistant to treatment. Relapses after mercury treatment are more frequent than with arsphenamine and bismuth and they occur soon after the active medication is discontinued.

Mode of action of mercury in syphilis. The mechanism of antisyphilitic action produced by mercury is not understood. Though the metal has direct lethal effects on the treponema, the concentration necessary to produce such lethal effects is never reached in the blood in doses which do not exceed the tolerance of the patients. Various theories have been advanced but none of them can explain the action satisfactorily. These include (1) direct toxicity to the parasites, (2) formation of antibodies or immune substances, (3) increased resistance by other factors, (4) increased susceptibility of the parasites to the protective mechanisms and (5) combination of all these factors.

Value of mercury in comparison to arsphenamine and bismuth. Syphilis can be promptly checked by chemotherapy, especially by the arsenic derivatives, almost as rapidly by bismuth, and somewhat more slowly by mercury, so that the treponema disappears from the lesions and the symptoms subside completely, at least in the early stages. As in other spirochaetal infections, recurrence is common unless the treatment is continued for some time. The permanent clinical cure of syphilis requires continuous energetic treatment for at least 2 years. Mercury, by whatever method it is administered, tends to produce cumulative effects and therefore periods of treatment must always be alternated with periods of 'rest'. Usually the drug is given for a period of 8 weeks, and then rest for one month is given. This process cannot be continued beyond a certain point, because symptoms of mercurial poisoning appear. To avoid symptoms of poisoning and to get the maximum effect,

it is best to alternate several antisyphilitic remedies instead of pushing unintermittently the same metal. This sort of alternation of the two drugs gives 'rest' to the patient without giving any respite to the parasites; the therapeutic effect is thereby enhanced by permitting higher dosage and probably also by attacking the parasites from several angles. Arsphe-namine, and mercury or bismuth are therefore given on alternating courses. Arsphe-namine is more rapid in action and is therefore used at the beginning of a course whereas mercury effects appear to be more thorough and more persistent. Bismuth is intermediate between mercury and arsphe-namine in rapidity and perhaps in power. Bismuth causes less pain on intramuscular injection and is less liable to set up serious stomatitis. On this account, it has practically displaced mercury in venereal diseases clinics.

Prophylactic use of mercury. Mercury has been used as a prophylactic remedy in syphilis for a long time. It often prevents the onset of primary and secondary lesions, if applied locally before the treponema have penetrated, *i.e.*, within 4 or at the most 8 hours after exposure. It has no preventive action 12 hours after exposure. The usual procedure recommended is to cleanse the site of the suspected infection with soap and dress the part with an ointment containing 33 per cent. of calomel or 0.3 per cent. of corrosive sublimate (Neisser-Seibert ointment). Schlossberger (1931) found that the prophylactic substances containing mercury prevented the dissemination of the spirochaetes through the scarified skin of mice only if the applications preceded that of the treponema; they were totally ineffective if applied even immediately after inoculation with the organism. This suggests that prophylactics containing mercury do no real good but may do harm by preventing the recognition of infection. This view however has not been supported by other workers who believe that mercury has got some prophylactic value if applied within 4 hours after exposure.

As a diuretic. All mercury compounds during their excretion stimulate the renal epithelium and produce a distinct diuretic effect. This diuretic effect is particularly marked when

there is oedema of the tissues. This property of mercury was known long ago and clinically made use of in the form of Guy's pill which is a combination of blue pill (*pilula hydrargyri*), with digitalis and squill. The diuretic effect of calomel was however unreliable and the diarrhoea set up during its administration was a very objectionable feature to the patients. Within recent years a number of stable organic mercury compounds have been prepared (see detailed description later on) which are soluble in water, practically non-irritant and non-toxic in therapeutic dosage, and can be used both intramuscularly and intravenously. Salyrgan (*Mersabyl*) and Novasurol (*Merbaphen*) are two well-known members of this group.

In cases of ascites following malaria and kala-azar, organic mercurial preparations have sometimes produced marvellous results. The excretion increases within 2 or 3 days of the administration of the drug and this increase is maintained for 6 to 7 days. These preparations have also been used in oedema following anaemia and hookworm disease. In the endemic ascites of the tropics, so commonly met with in Bengal and Bihar, novasurol and salyrgan have been given a trial in the Carmichael Hospital for Tropical Diseases. Megaw was of opinion that this condition was the end-result of bacillary dysentery and similar intestinal disturbances. Whether bacillary dysentery or avitaminosis is the principal factor concerned has not been determined, but experiences of various workers both in the School of Tropical Medicine and in the hospitals of various provinces in India definitely indicate that it is worth while to give mercury preparations a fair trial in these conditions.

In septicæmic condition. The antiseptic action of mercury has been utilised in the treatment of various septic processes, *e.g.*, septicæmia, pyæmia, erysipelas, puerperal fever, and septic sore-throat. Injections of mercury benzoate, 10 c.cm. of 1 per cent. solution have been given in many septicæmic conditions to disinfect the blood and tissues.

Young and Hill (1924) gave perchloride of mercury in doses of 2 to 5 mgm. per kilo. body weight in 1 per cent. solution in water, successfully in puerperal sepsis. Dudgeon (1926) tried perchloride in 330 cases of acute bacterial infections

such as influenza pneumonia; 5 c.cm. of a 1 in 1,250 solution of normal saline was given as the initial dose, repeated if necessary in 12 to 24 hours, according to the condition of the patient. Thrombosis, diarrhoea, stomatitis and nephritis were some of the complications encountered in his series of cases. Pritchard (1927) treated pneumonia both lobar and lobular, acute staphylococcal infections, chorea and subacute rheumatism, chronic infective arthritis of undetermined origin and encephalitis lethargica with injections of mercuric chloride (1/64 to 1/16 gr. in 8 to 10 c.cm. of normal saline) with fairly satisfactory results. Mercurochrome is another mercury preparation which has been widely used in septicæmic conditions. Encouraging results have been reported in puerperal sepsis. Following the routine use of mercurochrome intravenously in lobar pneumonia the mortality rate in Puerto Castilla Hospital, Honduras, was lowered by 12½ per cent. in 1925. Doses varying from 1.5 to 2 c.cm. of a 1 per cent. solution per 100 lb. body weight were usually given. The use of mercurials in septicæmia is however not unattended with danger. Reactions of the nature of colloidal shock have been reported which may lead to disastrous consequences.

Skin diseases. Mercury has been applied externally in various skin diseases of parasitic origin—such as itch, ulcers, condylomata and ulcers of syphilitic origin. In all these conditions, mercury acts as a disinfectant and irritant. Ointments containing mercury in metallic form such as unguentum hydrargyri are the least irritant of all. Mercury oleate, yellow oxide, red oxide and ammoniated mercury are also commonly used. As a lotion, black wash or yellow wash is the common external application; as a dusting powder calomel may be used on ulcerating surfaces, *e.g.*, in corneal ulcers.

Gonorrhœa and gleet. Mercury has been used as a lavage in urethritis, a lotion of 1 in 4,000 to 1 in 2,000 of mercuric chloride being commonly employed. Mercurochrome has been used intravenously in many cases of acute gonorrhœal infection. Redewill and Potter (1920) reported a high percentage of apparent cures within a very short time. Cases complicated with epididymitis, synovitis, arthritis, etc., have also been

successfully treated. Cystitis and pyelitis of gonococcal origin have been relieved.

Asthma and hay fever. Mercury has been found useful by some observers in hay fever, asthma and bronchiectasis. Injections of mercury salicylate, 1 per cent. suspension in oil, have been given for relief of the attack; $\frac{1}{2}$ gr. of calomel has also been used during the premonitory stages of an attack of asthma. These observations, however, have not been widely corroborated.

Bilharziasis. Bilharziasis has been treated with intravenous injections of mercuric chloride. In the early stages of the disease where anæmia is not marked mercurochrome is reported to have given satisfactory results.

MODES OF ADMINISTRATION

Mercury is administered chiefly by (1) inunction, (2) the mouth, (3) intramuscular injection, and (4) intravenous injection. All these methods have their special advantages and disadvantages.

Inunction. Mercury when triturated with fat forms a colloidal suspension which is rapidly absorbed when rubbed on the skin. Histological examination of the skin after inunction with mercury shows that the mercury globules do not enter the epidermis, but that they penetrate deep into the sweat glands and hair follicles and from there they are absorbed. It is a fairly effective method of administering mercury. Undesirable local and gastro-intestinal effects are not noticed and it is easy to avoid serious overdosage. The disadvantages are that it is time-consuming and disagreeable and the exact amount absorbed cannot be accurately determined.

In the United States Pharmacopœia there are two preparations, 'Stronger mercurial ointment' (50 per cent.) and 'Milder mercurial ointment' (30 per cent.) which are used for inunction purposes. An inunction course usually consists in inunctions being given six times a week for four to six weeks. This is followed by a rest for a month, and then the treatment is repeated.

Oral administration. The oral route is the easiest method of administering drugs but it is not suitable in the case of

mercury and has now been largely replaced by other methods in adults. In the case of children, this method is still retained for the sake of convenience. Considerable quantities of mercury can be absorbed from the gastro-intestinal tract even when the insoluble mercurous compounds are administered. This is proved by the incidence of salivation and the urinary excretion which is quite as high as with inunctions and intramuscular injections. The gastro-intestinal irritation is the serious drawback which has restricted oral administration. The patient also cannot be kept under control and the rate of absorption cannot be determined with any degree of accuracy.

Mercury can be given orally either as a solution of a soluble mercury salt or as a pill containing an insoluble mercurous salt or as metallic mercury. The usual preparations used, in order of preference are *Hydrargyrum iodidum flavum* (Proto-iodide) dose 0.01 to 0.05 gm. ($\frac{1}{4}$ to 1 gr.); *Hydrargyrum cum creta*, 0.05 to 0.2 gm. (1 to 8 gr.); *Hydrargyrum subchloridum*, 0.05 to 0.1 gm. *Hydrargyrum chloridum corrosivum*, 0.002 to 0.004 gm. (1/32 to 1/16 gr.). To prevent local corrosion, mercuric chloride is administered with excess of potassium iodide or in milk.

Rectal administration, fumigation, inhalation of mercury vapourized at room temperature are no longer used in practice.

Intramuscular injections. Three classes of preparation are used for intramuscular injections: (1) water-soluble ionizable compounds, (2) water-soluble non-ionizable compounds, and (3) water-insoluble compounds.

Water-soluble ionizable compounds. Lewin in 1867, first injected mercury intramuscularly and used a watery solution of mercuric chloride. Mercuric chloride (1 c.cm. of 1 per cent. solution) injections are very painful and should not be used. In general, all these salts are objectionable because pain and sloughing of tissues may follow, though some salts like the benzoate, succinimide, cyanide, biniodide (double salts) cause comparatively less pain than mercuric chloride.

Basic mercuric salicylate is insoluble in water but is soluble in sodium chloride solutions or alkalis. It is given suspended in oil but is absorbed as rapidly as the water-soluble salts. It causes very little pain.

Water-soluble non-ionizing compounds. These include novasurol, nalyrgan and mercurisol. The antisyphilitic action of the first two is practically negligible. They cause very little local irritation and are not toxic in therapeutic dosage. The absorption is very rapid and

fairly complete. These are used as diuretics and will be referred to again.

Water-insoluble compounds. These compounds are usually given suspended in oil. Although these are highly effective, they are now practically out of use. Their absorption is slow, since they must first be converted into soluble compounds; but when the injections are repeated, the absorption from the multiple depots becomes cumulative and uncontrollable. Stomatitis is a frequent complication. Calomel 10 per cent. suspension in olive oil in dosage of $\frac{1}{2}$ c.cm. weekly to 1 c.cm. twice weekly is used. Calomel has also been injected as a 5 per cent. suspension with 2 per cent. carbolic acid or creosote or camphoric acid. Metallic mercury, finely divided, as the 'gray oil' (oleum cinereum) has been injected in 40 per cent. solution, $\frac{1}{2}$ c.cm. weekly.

Intravenous injections. Intravenous injections of mercury were introduced by Bacelli with the idea of securing a maximal concentration of mercury in the blood without any of its unpleasant and untoward local actions. These however have not attained any degree of popularity. Preparations for intravenous injections may be conveniently studied under two groups.

(1) **Ionizable salts.** Mercuric chloride, oxycyanide, benzoate and the double iodide have been administered in 1 per cent. solution in doses of 1 to 3 c.cm. daily or every second day. With mercuric chloride it is advisable to add 3 per cent. of sodium chloride to the solution. The therapeutic results in syphilis following the administration of these compounds are not at all encouraging, at least no special benefit is reported by this method. Strickler (1923) who tested the efficacy of this method found no change in the Wassermann reaction after 37 intravenous injections of the benzoate. The chief difficulty appears to be that the metal is rapidly excreted and does not maintain a concentration in the blood sufficiently high to be lethal to *T. pallidum*. The study of the urinary excretion proves this point conclusively. In a series of experiments, Lomholt found that the excretion rose to a peak in one or two hours after each injection, which is about ten times the average level after intramuscular injections.

(2) **Organic compounds.** Novasurol, salyrgan, mercurosol have been used to a much greater extent than the ionizable mercury salts. As has been already stated, these compounds are not very effective in syphilis and their chief use is in connection with the production of diuresis. With these compounds, as with ionizable salts, urinary excretion of the metal proceeds at a rapid rate within an hour or two, and declines promptly, reaching an insignificant level within 8 hours after injection. These therefore suffer from the same disqualification as the other group. Moreover, novasurol and mercurosol

produce diarrhoea and dysentery-like symptoms in some patients. Salyrgan is not reported to have caused any untoward symptoms. The mercurial dye flumerin occupies a peculiar position amongst the organic mercury compounds. Like other dyes, it tends to form colloidal absorption products with proteins. In experimental rabbit syphilis, promising results have been obtained but it is not superior to the ordinary mercurial treatment.

Apart from these two groups, mercury in colloidal form has also been injected intravenously. A true colloidal solution of mercuric sulphide known as *Mersufol* (2 per cent. solution) is available in the market. This preparation has the advantage over others in that the excretion of the metal is not very rapid, in fact a good deal of mercury is retained, even after four weeks following its administration. This would have proved quite a useful preparation but for the fact that considerable salivation is produced in the patients and the mobilization of the metal cannot be controlled. *Mercodel* is another preparation which is not colloidal but is a water suspension of fine sub-microscopic globules of mercury to which a little glucose is added. With doses larger than 200 mgm. per week, it is an effective drug but serious stomatitis is a frequent complication. Smaller doses, though free from undesirable side-effects, are useless.

Disadvantages of intravenous administration. It will be seen from the above that intravenous administration of mercury is not the method of choice and is not as effective therapeutically as the intramuscular method. Most of the compounds irritate the veins at the site of injection and tend to produce fibrosis and occlusion of the vein. They also present some danger of embolism and colloido-clastic shock. Urinary excretion studies indicate that the high concentration reached by intravenous injection is of too brief a duration to be useful in chemotherapy and the maintained level is generally too low, even with daily injections. The organic and inorganic preparations are presumably fixed up in the tissues and remain inactive to a large extent. The colloidal compounds are probably enmeshed in the reticulo-endothelial cells, forming depots from which active mercury is absorbed and circulates for long periods but the absorption is variable and is uncontrollable, giving rise to severe untoward effects in most cases.

CHAPTER XXXVI

TOXIC EFFECTS OF MERCURY

Acute toxic manifestations are produced, generally from mercuric chloride poisoning. The immediate effects are due to irritation, superficial corrosion and coagulation of the proteins of the mucous membranes. Salivation, swelling, burning and discolouration of the mucous membrane of the mouth and pharynx are constant features. Abdominal pain and distress with vomiting of bloody mucous shreds are also met with. Twenty-four hours later, mercurial stomatitis develops but this is not very severe. Later, the large intestine and kidneys become involved. The urine becomes scanty and highly-coloured with copious albumin and casts. Anuria has occurred in some cases followed by death within a week. If the nephritis is not fatal, a membranous colitis develops with ulceration and hæmorrhage. Hepatic degeneration may supervene. Death occurs from circulatory failure in some cases.

Post-mortem examination shows the mucous membranes of the mouth, pharynx, glottis, œsophagus and stomach to be corroded and extremely congested. In the colon, necrosis and ulceration and consequent congestion are met with. The kidneys show signs of acute nephritis and the liver cells are degenerated in some cases.

The symptoms of acute mercurial poisoning are not produced in therapeutic doses of the drug and are therefore not very important from the clinical standpoint. A sort of subacute mercurial poisoning is the usual outcome of prolonged treatment. The symptoms which have to be guarded against by the physician in such cases are of a milder nature and consist of localised chronic inflammations, especially stomatitis, colitis, nephritis, etc. The stomach and large intestines are usually not involved as in the case of acute poisoning.

Stomatitis is usually the earliest symptom of subacute and chronic mercurial poisoning. It occurs constantly by whichever route mercury is administered. A metallic taste in the mouth, soreness of the gums and salivation are the primary manifestations. If not noticed in time and if the drug is pushed further, blackening of the gum margins, loosening of the teeth, uncontrollable salivation and later, fatal ulceration of the mouth may supervene. The kidneys are specially susceptible to mercury and therefore albuminuria is a common finding. The damage however is not as marked as in cases of acute poisoning and tends to involve the interstitial cells more than the glomeruli. Long-continued exposure to relatively small doses leads to a slow and insidious development of chronic poisoning, usually with some stomatitis and renal irritation, but with additional nervous and nutritional disturbances. Cachexia with anæmia and malnutrition are found together with psychic irritability, tremors and restlessness.

Treatment of mercurial poisoning. The prognosis in cases of acute mercurial poisoning is grave unless prompt emesis is resorted to within 15 minutes of the administration of the poison. Mercury is rapidly fixed in the mucous membrane of the stomach and once it gets fixed, the antidotes (milk, calcium sulphide, thiosulphate, etc.) naturally cease to react. Lavage is sometimes helpful by removing the mercury which may remain free in the stomach at the time. The simplest antidote consists of three raw eggs in a quart of milk followed by gastric lavage. The local antidotes must be followed by an emetic to expel any poison which might remain unabsorbed. Administration of glucose and alkalies is useful and hot packs in the kidney region may help in soothing the renal irritation. Sodium thiosulphate has been advocated intravenously but is not very satisfactory.

In subacute cases, stomatitis and colitis are the symptoms to be attended to. Stomatitis is most effectively prevented and treated by hygiene and care of the teeth. Septic conditions about the gums are especially liable to cause poisoning and should be attended to before mercury treatment is started. When stomatitis is very severe, mercury should be stopped and

mouth washes and gargles of an antiseptic nature should be prescribed. Hydrogen peroxide, potassium chlorate, potassium permanganate are all useful and should be used several times a day. The gastro-intestinal troubles usually yield to sedatives such as chalk and bismuth. Stimulants, whenever necessary, should be given.

Cases of chronic mercurial poisoning seen in workers in mercurial mines, etc., cannot be much improved even with vigorous treatment. In these cases, prevention and protection against unnecessary exposure are more important.

PREPARATIONS OF MERCURY

The preparations of mercury which are recognised in the British Pharmacopœia are too well known to require any detailed description. In recent years attempts have been made to improve mercurial therapy and a number of organic compounds have been prepared. As these compounds are coming into prominence in the treatment of various conditions commonly met with in the tropics, it will be worth while to discuss them in some detail.

MERCUROCHROME 220

Mercurochrome is disodium-dibromo-hydroxy mercury fluorescein, and was prepared in 1920. Dose 0.002 to 0.003 gm. per kilo; in man 2 to 5 gr. (0.18 to 0.82 gm.). It is given intravenously in the form of 0.5 per cent. solution in distilled water. Though solutions of 1.0 per cent. and of higher strength have been recommended, they are not desirable. Mercurochrome 'sterules' containing 0.2 gm. dissolved in 40 c.cm. of water for intravenous use are on the market.

Pharmacological action. Mercurochrome has a well-marked disinfectant action and is largely employed as a general antiseptic in surgery. A 2.5 per cent. solution is useful for surface lesions, for painting on the mucous membranes or for injection into sinuses. Given intravenously in animals, mercurochrome causes no marked reaction if a 0.5 per cent. solution is used. Stronger solutions produce a fall of blood pressure. Administration of 0.2 mgm. per gm. weight of mice produce immediate death of the animal. Small doses are therefore recommended in man and deaths have occurred with 8 to 15 c.cm. of a 1.0 per cent. solution. It is absorbed into the blood and is excreted in the gastro-intestinal tract, in the bile and by the kidneys. It is, for this reason, used as an urinary and biliary antiseptic. Bile collected after intravenous injections is said to have definitely bactericidal properties, but this has not been proved. Large doses irritate the kidneys as well as the intestines and produce diarrhœa. Kofoed and Wagner (1925)

found that 1 in 11,000 of mercurochrome has a lethal effect on cultures of *E. histolytica*; 1 in 3,500 inhibits the growth of *B. coli* in nutrient broth, 1 in 8,000 inhibits growth of hæmolytic streptococci.

Therapeutic uses. Mercurochrome is recommended in all forms of bacterial diseases. It has been used in gonorrhœa, gonorrhœal arthritis, cystitis and pyelitis with good results. As a vesical antiseptic 1 per cent. solution can be used for lavage without causing any pain. It is very penetrating and has a low toxicity. Young and others (1921) obtained a cure rate of 75 per cent. in chronic cystitis with this drug. The routine method of giving vesical injections is to give 30 c.cm. of a 1 per cent. solution, stronger solutions should be used with great caution. A 5 per cent. solution as a urethral lavage can be relied upon to clear up gleet in most chronic cases, and great improvement has been noticed after treatment. Gonorrhœal arthritis is said to be favourably influenced by intravenous medication for which 10 c.cm. of a 1 per cent. solution is generally recommended. It has also been tried in plague, pneumonia, Malta fever, puerperal septicæmia, syphilis, typhoid and tuberculous affections. Mercurochrome has been tried in the treatment of intestinal protozoal infections. It is given by the mouth in 1 to 5 gr. (0.13 to 0.23 gm.) doses three times a day, the drug being continued for 2 or 3 weeks. It is germicidal and penetrating and forms no precipitate with the proteins. It is usually given in keratin-coated capsules and no harmful or distressing effects have been observed. Encouraging results are also said to have been obtained in amœbic dysentery as well as in *Giardia* and *Chilomastix* infections. The stool changes into a deep mahogany colour and must be kept thus so long as the drug is administered. Rarely, the drug produces intestinal cramps and nausea.

Mercurochrome has also been used in the form of colonic irrigations, a 5 per cent. solution being injected slowly into the rectum in amœbic dysentery. In ulcerative colitis lavage with 6 to 8 ounces of a 0.3 per cent. solution has given good results. It has been used against leprosy for checking rapid retrogression, in the treatment of ulcers following on disintegrating tubercles and in healing neurotropic ulcers, weekly injections of 1.0 per cent. solutions are generally given. Good results have followed by combining it with chaulmoogra oil esters. It has also been tried in malaria, especially the chronic forms, but has no effect in this disease. In relapsing fever 15 c.cm. of a 1.0 per cent. solution produced a fall of temperature and no further recurrence of attacks.

Tootell (1926) tried the drug in the early stages of schistosomiasis where no serious complications were present, and obtained good results. The author tried mercurochrome in filariasis but found it to be useless. In yaws, marked improvement has been obtained by two injections of 5 c.cm. of a 2.5 per cent. solution. The lesions healed quickly.

Given intravenously the drug is claimed to have given good results in general septicæmia, puerperal fever, diffuse cellulitis, lobar pneumonia, typhoid, pyelitis and many other conditions. The maximum dose is 10 c.cm. of a 0.5 per cent. solution in saline. The rigors which follow intravenous injections may be greatly modified by keeping the patient warm during and after treatment and by giving 10 gr. of aspirin with hot tea immediately after injection. Intravenous injections of mercurochrome with glucose are said to be less toxic than mercurochrome alone, but it is insisted that the glucose mercurochrome mixture should be made immediately before use. While some workers have found the drug to be very effective in septicæmia, others find it has little or no effect. Human blood treated with mercurochrome (1 in 40,000 to 1 in 10,000) has no bactericidal power for staphylococci and hæmolytic streptococci. Bile from rabbits treated with 5 mgm. of mercurochrome showed no bactericidal power for *B. typhosus*. It has been suggested that the remarkable clinical improvement in some septicæmic patients is brought about by an auto-immunisation process initiated by severe constitutional symptoms which may follow the injection of the drug. The results would thus be analogous to protein shock. In secondary syphilitic manifestations injection of 5 to 10 c.cm. of a 2.5 per cent. solution has given good results, but the effects are inferior to arsphenamine or bismuth.

Toxic effects. The toxicity of different samples varies. Salivation, stomatitis and severe diarrhoea, commonly nausea and vomiting, rose-coloured stools, rigors and rise of temperature may occur after large doses. The kidneys may be irritated and albumin may occur in the urine. The margin between the therapeutic and toxic doses of mercurochrome is variable and small. As a rule no gastro-intestinal disturbances are produced till the drug has been continued for a week. Idiosyncrasy and hypersensitiveness to mercurochrome may rarely occur. Such patients excrete a greater quantity of mercury by the saliva and the gastro-intestinal tract than by the kidneys. In these individuals most of the drug appear to be excreted by the gastro-intestinal tract and not by the kidneys and signs of mercurial poisoning are quickly produced.

A number of other preparations of mercury and dyes have been produced, e.g., *mercurochrome 565* which is a mercury derivative of rose-benzol 3B and benzurine. It is still in the experimental stage.

FLUMERIN

Flumerin is the disodium-hydroxy-mercuri-fluorescein. It is a red odourless powder, somewhat hygroscopic, containing 83 per cent. of mercury. It is soluble in hot water, about 1 in 10, but insoluble in alcohol, ether or chloroform.

Pharmacological action. Flumerin is an antiseptic. It is far less toxic than other compounds when given intravenously in animals. It is liable to produce irritation of the kidneys on repeated administration. It is tolerated by rabbits in doses which are about 8 to 20 times higher, calculated according to mercury content. According to some workers, when given intravenously in man in doses of 3 mgm. per kilo. body weight, the drug causes disappearance of the spirochaetes from primary and secondary syphilitic lesions. The influence on the Wassermann reaction was also encouraging, rendering one-half of the positive cases negative within a short time. In tertiary syphilitic lesions the resolution of the lesion and the disappearance of a positive Wassermann reaction were brought about in a majority of the cases. Snodgrass (1924) also obtained improvement of gross secondary lesions within one week of the administration of the drug. The influence on the Wassermann reaction was not a lasting one. Great toleration to the drug was noted. Moore and Wassermann (1924) suggest the combined use of arsenobenzol and flumerin. They advise a course of 8 injections of arsenobenzol at 5 to 7 days intervals, then one week later 12 flumerin injections every other day; this is immediately followed by 6 injections of arsenobenzol and one week later by 16 injections of flumerin.

Toxic symptoms have been noticed with the drug. These are salivation, and gingivitis and are not generally fatal. Damage to the kidney is sometimes liable to occur, especially in cases where there are pre-existing kidney lesions.

The dosage for adult males is from 0.2 to 0.3 gm. given in 2 per cent. solutions intravenously at bi-weekly intervals, the average number of injections necessary being 8 to 10. In no case should more than 0.3 gm. be given at a time for fear of toxic symptoms supervening.

NOVASUROL

Novasurol is also known as merbaphen; it is the double salt of sodium mercuri-chlorphenyl oxyacetate with diethyl barbituric acid (barbital). Novasurol occurs as a white crystalline powder, soluble in cold water and contains about 34 per cent. of mercury.

Pharmacological action. Novasurol was originally intended to be an antisymphilitic remedy but has come to be used as a diuretic. It has the advantage over mercurous chloride that it is soluble in water and can be advantageously given intramuscularly or intravenously. When given intramuscularly it is excreted in the gut and doses higher than 2 c.cm. are liable to cause gastro-intestinal irritation with profuse watery stools.

The action of novasurol on the kidneys is important, since it has been extensively used in cases of nephritis with oedema. The beneficial effect is more marked in oedema due to myocardial insufficiency than in

cases of nephritis, where it is contraindicated. The exact mode in which novasurol brings about diuresis is not known. It is believed by some to be the result of a combined action on the kidney and extrarenal tissue. Bohn (1923) believed that extrarenal mobilization of fluid is the most important factor in the diuresis produced. Jackson (1928) showed that changes occur in the volume of the kidney after administration of novasurol and he considers that the diuretic effect is related to the vascular changes brought about in the kidney, possibly causing greater contraction in the efferent than in the afferent glomerular capillaries.

Toxicity. Johnstone and Keith (1928) found that in rabbits doses of 0.7 c.cm. per kilo. killed the animals within a few minutes and death was assumed to be due to ventricular fibrillation or to a direct effect on the vital centres in the medulla. A dose of 0.168 c.cm. per kilo. was lethal. Repeated doses were consistently toxic and the kidneys showed characteristic degenerative changes. These consisted in the early stages of swelling of the epithelium, specially of the proximate convoluted tubules. Larger doses produced extensive degeneration involving wide areas.

In man, toxic symptoms have occurred after novasurol. In mild cases, certain disagreeable symptoms such as headache, vertigo, nausea, vomiting, stomatitis, diarrhoea, fever and rash are seen. These symptoms are generally mild and clear up with the discontinuance of the drug. In certain cases hæmaturia has occurred; death from the effect of novasurol is also on record.

Therapeutic uses. It is useful in dropsies due to cardiac and cardiorenal diseases. It has been recommended in passive congestion of the kidney's, in nephrosis, and in arteriosclerotic and idiopathic contracted kidney. Ascites due to cirrhosis of the liver and Banti's disease is not usually benefited by the drug. As a diuretic 0.5 to 1 c.cm. of a 10 per cent. solution is advised. Rowntree and his co-workers (1925) advise simultaneous administration of ammonium chloride with novasurol, to improve the diuresis. As an antisyphilitic remedy the initial dose is 0.75 c.cm. or 1 c.cm. of 10 per cent. solution injected intramuscularly once or twice weekly, later the doses should be increased to 2 c.cm. More recently, 1 c.cm. of a 10 per cent. solution of novasurol, mixed with the required dose of arsphenamine has been used intravenously in syphilis. This is repeated every 5 days for about 3 injections.

SALYRGAN

This is another member of the organic mercury compounds which has been used in recent years very extensively in cardiac or renal oedema, to produce diuresis. It is a complex synthetic mercurial prepared by the action of mercury acetate and methyl alcohol on

salicyl-allyl-amido-acetic acid and subsequent conversion to the sodium salt. The mercury content is about 40 per cent. in non-ionizable form. It is a white crystalline powder, soluble 1 in 1 of water. It has been demonstrated to have spirochaetocidal properties. The diuretic property of the drug is well known.

Salyrgan has been used in a great variety of conditions: (1) Cardio-renal oedema, (2) nephrosis, (3) malignant conditions with ascites, (4) cirrhosis of the liver, (5) tubercular peritonitis, (6) pleurisy with effusion, (7) malignant conditions with chylous pleural effusion.

The advantages claimed for the drug are that stomatitis and proctitis, common with merbaphen, do not occur with salyrgan. Brunn (1924) reports diuresis of from 3 to 4 litres after the use of the drug in 27 patients with oedema as a result of various cardiac disorders. No ill effects were seen and no increase of albumin in the urine was noticed. Herszky (1925) observes that salyrgan is effective occasionally, when merbaphen fails and he has not found any single case of mercurial intoxication. Jacobs and Keith (1926) suggested the use of ammonium chloride and nitrate with mercurials in order to raise the diuretic response.

The mechanism of salyrgan diuresis is difficult to explain. Richards (1925) believes that intraglomerular pressure, which is so important in urine formation, is under a very delicate balance of control in case of cardiac or cardiorenal oedema and that the tension on the afferent artery is probably not more important than the tone of the efferent vessel in maintaining this glomerular pressure. It is probable that the diuretic effect of salyrgan is due to this vascular response with an increase of pressure in Bowman's capsules. Jackson (1926) showed that respiration is accelerated, the blood pressure rises slightly and the kidney volume decreases. He thinks that the action of mercury preparations is on the vascular structure of the body and that the diuresis is related to a vascular response.

Mercuriol. Mercury nucleinate is the organic compound of mercury with nucleinic acid, containing about 20 per cent of mercury. Mercuriol has a powerful antiseptic property. It is markedly bactericidal and does not coagulate albumin which ensures better penetrability and intimate contact with organisms. It resembles in general, the action of soluble mercury compounds. It is used as a local antiseptic and as an antisyphilitic remedy. Dosage is 0.08 to 0.12 gm. by the mouth in the form of tablets.

Mercurosal. This compound is the disodium-hydroxy-mercuri-salicyl-oxy-acetate, containing from 48 to 44 per cent. of mercury. Mercurosal is a white amorphous powder. It is soluble in about 10 parts of water. It is fairly stable in aqueous solutions and should be kept well-stoppered and protected from air. It is claimed to be a relatively non-toxic compound and that it is eliminated without producing any

damage to the kidneys and at the same time, its toxicity is much lower than either mercuric chloride or salicylate. It does not coagulate albumin.

The dosage recommended in syphilis is 0.05 gm. dissolved in 2 c.cm. of water every fourth or fifth day, a total of ten or twelve injections being necessary.

Mergol. It is a mixture of 1 part of mercuric cholate and 2 parts of albumin tannate. It is put up in capsules each capsule containing approximately 0.15 gm. of mergol, equivalent to 0.05 gm. of mercuric cholate and 0.1 gm. of albumin tannate. Mergol contains about 44 per cent. of mercury.

Mergol is said to pass through the stomach unchanged and is decomposed in the small intestine from whence the mercury is quickly absorbed into the circulation. The main channel of excretion of mercury is through the kidneys. It is employed in the treatment of syphilis, given in doses of one capsule three times a day after meals gradually increased to 2 capsules five or six times a day.

Meroxyl. It contains 50 per cent. of sodium-2:4-dihydroxy-3:5-dihydroxymercuri-benzophenone sulphonate with foreign matter consisting of ammonium-dihydroxy-benzophenone-2-sulphonate, sodium acetate and water. The mercury content varies between 26 to 29 per cent. Young and others (1923) recommend meroxyl as a local antiseptic for dressings and irrigation of wounds and for gonorrhoeal cystitis and abscesses a 0.1 per cent. solution is preferred as an antiseptic. For prophylactic treatment of urinary infection 0.5 per cent. solution should be used. Solutions of 2.5 per cent. or stronger form a gel on standing.

Metaphen. This is diacetoxy-3:5-mercuri-4-nitro-2-cresol. It contains about 58 to 60 per cent. of mercury. Metaphen is a yellow substance, insoluble in water. It is a powerful germicide. Rabbits experimentally infected with *staphylococcus aureus* are beneficially influenced by the drug 48 to 72 hours after the infection. On the intact skin and mucous membrane it is stated to be relatively less toxic than other organic preparations. White rats can tolerate doses of 0.03 gm. per kilo. body weight when injected intramuscularly and 0.004 gm. per kilo. when given intravenously. For disinfectant purposes and for sterilising the skin solutions of 1 in 5,000 to 1 in 1,000 are prepared with the aid of caustic soda; for ophthalmic purposes solutions of 1 in 10,000 to 1 in 5,000 are preferred. Urethral lavage should be done with solutions of 1 in 10,000 to 1 in 5,000.

2-Myristoxymercuri-3-hydroxybenzaldehyde. This is an organic preparation of mercury prepared by Henry and Sharp of the Wellcome Research Laboratories. This preparation is easily soluble in hydnocarpus oil and is practically non-toxic. Dissolved as a 0.25 per cent. solution in hydnocarpus oil, the preparation is known as 'avenyl'. Mair

(1926) found that hydnocarpus oil alone produced no effect on the Wassermann reaction and he was able to give as much as 10 c.cm. of this compound twice weekly for 15 doses without producing toxic symptoms of any kind. Of 30 leprosy patients with positive Wassermann reactions treated with avenyl, sixteen were rendered negative. In a further paper Lloyd, Muir and Mitra (1926) state that they have never encountered unpleasant reactions or toxic effects from the use of avenyl. Avenyl is therefore particularly suitable in leprosy patients with a syphilitic taint. In these cases, organic arsenicals are unsuitable and may frequently give rise to toxic manifestations and check the progress of leprosy treatment.

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PART IV

REMEDIES USED AGAINST BACTERIAL DISEASES

CHAPTER I

GENERAL CONSIDERATION

The bacteria are minute unicellular masses of protoplasm which are devoid of chlorophyll and definite nuclei. The dimensions of most of the cultivable forms of bacteria are of the order of low multiples or sub-multiples of μ or $1/25,000$ of an inch. In the living condition they are transparent, colourless and homogeneous. They are definite in shape, and are surrounded by a cell envelope which is a specialised part of the ectoplasm. All bacteria require for their growth a considerable amount of food material and water. There are certain types, belonging to the bacilli and spirilla groups which are motile, while others are motionless. Some are provided with flagella all round the body, in others these may be present at one or both ends. The lower forms of bacteria have no special reproductive structure, they multiply by simple fission and thus continue the species. If there is sufficient food material and conditions of temperature, oxygen, etc., are favourable, each individual organism divides into two, which again undergo similar division. Other forms of organisms are smaller and are ultra-microscopic and filter-passing. Certain bacteria, the so-called higher bacteria, come midway between the lower bacteria and the fungi and exhibit specialised reproductive structures; this suggests that they are probably closely related to the plants.

Certain bacteria which form spores have the power of protracted survival under unfavourable conditions. It is important to bear in mind that for the existence of many of the pathogenic bacteria some animal host is necessary, and except perhaps the resistant spore-bearing forms, they do not survive very long in nature apart from the bodies of animals which they invade.

All bacteria are not pathogenic and those that are pathogenic cause disturbance of health with the development of lesions which may be localised or may be disseminated throughout the body. Certain pathogenic organisms, *e.g.*, *Bact. typhosum*, *V. cholerae*, can be present in the body without manifestations of disease. Other bacteria such as *Bact. coli* are normal inhabitants of the intestine but under certain conditions become pathogenic.

The popular conception that the presence of bacteria is always associated with disease is erroneous. Human life would have been impossible were it not for the innumerable activities of bacteria which are definitely beneficial. Moreover, the bacteria found on the exposed parts of our bodies, such as *Bact. coli*, staphylococci and diphtheroid bacilli are of common occurrence. The nostrils serve as a filter for inspired air and the bacterial flora found there include varieties of cocci and bacilli; in the throat, streptococci and staphylococci are found even in the absence of any obvious signs of disease. The alimentary canal presents a highly complex bacterial flora. In a normal healthy person the stomach is comparatively sterile owing to the presence of hydrochloric acid, but the lower intestines contain an enormous variety of bacteria. *Bact. coli* and the proteus group, are present in large numbers in addition to others such as *streptococci*, *B. mesentericus* and various spore-bearing anaerobic bacilli.

The types and number of these bacteria are liable to great variations and to a great extent with the diet. The relative proportions of various organisms are variable and these organisms are compatible with a normal state of health. They are, however, potentially dangerous. *Bact. coli* in the intestine is non-pathogenic, but it may occasionally become pathogenic, as a result of imperfect nutrition, exposure to cold, interference with blood supply and some other conditions in the body of the host. In such conditions the organism invades the body and sets up pathological changes, such as, cystitis, peritonitis, etc. Streptococci in the mouth and throat may similarly cause harm and may give rise to endocarditis and arthritis. Many other bacteria which occur normally about the body may similarly be potentially pathogenic.

The bacteria which are pathogenic mostly live outside the body and then gain entrance into the body of the host. When they reach a suitable place they multiply, produce the specific disease and escape from the body and find another victim. The methods by which infection is produced are interesting. The majority of the epidemic and endemic diseases spread directly or indirectly from one individual to another. In some cases the infected person, after recovery from the illness, harbours the causative organism, in which case he is termed a 'carrier'. The carrier condition is often present during convalescence, but it is generally not of long duration, the organism being eliminated soon after the individual regains his normal health. In

the carrier condition the organism lives in harmony with the host producing no symptoms of disease, but it may still retain pathogenic properties for others. Such an individual is a constant source of danger to others.

The routes by which bacteria enter the body are various. The commonest infectious diseases, such as diphtheria, tuberculosis, etc., leave one host and enter into another by the respiratory tract. The sputum in droplets sprayed out from the mouth and nose contains infected material laden with these bacteria. Overcrowding and lack of adequate ventilation favour the infection of those whose powers of resistance are low. Another group of organisms gain entrance into the body by the mouth. Among these are the *V. cholerae*, *Bact. typhosum*, and organisms of dysentery group, which are chiefly spread by healthy carriers and by flies which feed on excreta and transfer the organisms to food. Venereal diseases, such as gonorrhoea and syphilis, are usually transmitted through direct contact between the person harbouring the organisms and the one about to be infected. Many other diseases, such as rabies in dogs, anthrax in sheep, and glanders in horses, are transmitted to man from the infected animals.

In order that a particular organism may cause an infectious disease, the association of a number of factors have to be taken into consideration. Briefly stated these are:—(1) The virulence of the specific organism, (2) the number of bacteria invading the host, (3) the channels of infection, and (4) the susceptibility and resistance on the part of the host.

Virulence of the organism. The virulence of an organism signifies its capacity to produce disease by overcoming the natural defensive mechanism of the host. The virulent bacteria have the power to multiply in the body and to produce toxic substances. Certain bacteria such as *C. diphtheriae* produce highly potent toxins but do not invade extensively, while *B. anthracis* is slightly toxic but has a greater power of invading the body. The virulence of an organism is liable to great modifications. It may be quite easily lost, for example, by growth in an artificial culture medium. On the other hand, it may be increased by passage through animals, that is, by transfer from one animal to another. The explanation of such heightening in virulence is that the virulent ones grow rapidly and readily in the animal tissue while the avirulent organisms tend to disappear with the result that the surviving strain contains a greater proportion of virulent bacteria.

The number of bacteria. To produce an infection it is necessary that a requisite number of bacteria invades the tissue. It has been shown experimentally that a single anthrax bacillus may cause fatal infection in about 28 per cent. of mice, while 10 anthrax bacilli are capable of destroying all the mice infected. Infection is most likely to develop when the invading organisms reach the host in large

numbers and frequently, and it is for this reason that epidemics of respiratory diseases, such as influenza, originate in thickly populated places.

Channel of infection. The route of entrance of the infective organism and the vector by which it is conveyed to the host are very important from the point of view of prophylaxis and treatment of diseases. Certain organisms, *e.g.*, *Bact. typhosum*, and the dysentery group of organisms enter by the mouth and the characteristic lesions due to those organisms are found in the intestinal canal. Thus it has been shown that direct inoculation of these organisms into the tissues is incapable of causing the disease. Other organisms such as the *C. diphtheriae*, *Fusiform fusiformis*, usually select the mucous membrane of the fauces and larynx as their primary sites of attack.

Susceptibility of the host exerts a marked influence on the course of the infection. So long as the chemical substances produced by the metabolism of the parasite are innocuous or helpful to the host, there will be no reaction against the invading organism. But certain organisms produce chemical substances such as toxins which damage the tissues of the host. In such cases, some reaction on the part of the host is bound to develop. It is probably rare for the bacteria to be present initially in such numbers or to possess so high a degree of virulence as to paralyse completely the natural defensive mechanisms of the host. Thus there is always a struggle going on between the natural defensive mechanism of the body and the invading organism; the more prompt and efficient the response of the host, the better is the outlook. There is good ground for belief that any agency which interferes with the general health of the patient or which damages the tissues of the host will diminish natural or acquired resistance to infection. Thus fatigue and chronic alcoholism cause a general deterioration of health; injudicious diet predisposes to disturbances of the alimentary canal and increases the susceptibility to bacterial infection; trauma mechanically opens a road into the tissues and creates a nidus for the growth and multiplication of the invading organisms.

CHEMOTHERAPY OF BACTERIAL DISEASES

Chemotherapy of infections with common bacteria such as streptococci, staphylococci, pneumococci, tubercle bacilli, etc., has been developed along two lines, (a) the employment of anti-septic substances whose antibacterial properties are relatively high as compared with their toxicity for animal tissues, and (b) the metal-salt therapy, the substances being used in doses which have probably no direct action on the organisms.

For a substance to be successful in killing bacteria in the circulating blood, two essential conditions must be fulfilled. It should, after injection, attain a concentration in the blood lethal to the microbes but at the same time be harmless to the host, and it must maintain such a concentration sufficiently long for the microbes to be killed.

If a germicide is introduced into the circulation, the concentration of the drug will be at its maximum immediately after the injection, and simultaneously with it, the bactericidal power will also be at its highest. If, on the other hand, there is no increased bactericidal power of the blood immediately after the injection, but only after a lapse of time, such an increase cannot be ascribed to the drug alone, but to some other factor. This is significant from the fact that normal human blood has got a great bactericidal property. It has been found that 1 c.cm. of human blood when incubated with 2,000 to 5,000 staphylococci can destroy 90 per cent. of the cocci. When chemotherapeutic substances are injected into the blood, the reaction that takes place is complex. These agents may act directly on the organisms so as to cause their death, or, their action may be an indirect one due to stimulation of the natural defensive powers of the tissues. Both these factors may come into play. If the vitality of the organism is lowered by direct action, then the cellular and humoral tissue defences may be enabled to come into play. Further the products resulting from the destruction of the organisms act as antigens, and in this way immunity reactions are developed.

While the treatment of protozoal and helminthic infections with chemicals has attained a considerable measure of success, the treatment of bacterial diseases, on the other hand, is still unsatisfactory. Most of the chemical bactericidal substances at present in use precipitate proteins and are therefore general protoplasmic poisons. They, therefore, destroy the resisting power of the tissues to infection. Moreover, they are rapidly removed from the circulation after an intravenous injection and hence the effect produced is of a temporary nature. In the case of wounds, the treatment with chemicals presents a complicated phenomenon. Experimental evidence that an antiseptic can

afford benefit by directly killing the organisms with which it comes into contact has been advanced, but it has not yet been accepted generally. The strength of such an antiseptic will rapidly fall below the concentration in which it has any bactericidal effect. On the other hand the harmful effects produced by the drug on the tissues, such as necrosis and damage to the leucocytes, outweigh its other action, so that the surviving bacteria are thereby able to propagate the infection more freely. Thus most of the antiseptic substances that are known, such as eusol, Dakin's solution and the antiseptic coal tar derivatives, lose much of their potency in a very short time.

Antiseptics have been tried in generalised and remote bacterial infections in the same way as therapeutic agents are now employed to destroy protozoa. It has been shown experimentally in animals that, after intravenous injection of various dye-stuffs, the blood becomes rapidly bactericidal and this property is retained for some time afterwards.

Koch first carried out a series of experiments with a number of drugs to produce disinfection within the body in cases of septicæmia. He tried mercury compounds, but these proved useless because they were inactivated by the proteins of the blood. Innumerable drugs have since been tried in bacterial diseases but the success has been very limited. Experiments *in vitro* do not always represent the results that may be obtained *in vivo*. Drugs having highly bactericidal properties *in vitro* do not necessarily ensure chemotherapeutic activity *in vivo*. Moreover the action of a drug in combating a bacterial infection of the tissues in animals cannot be applied *in toto* in clinical trials in man.

In this connection another important point has also to be considered. Different species of bacteria possess different powers of resistance to various drugs. Compounds of chlorine, phenol and mercury show considerable differences in their power to kill different bacteria, and their specificity can be greatly augmented or retarded by changes in their structure. For example, the halogen compounds of naphthol have been found to possess high bactericidal activity against *C. diphtheriæ* and *Bact. coli*. The coal-tar dyes also show marked specific

action and many of them have been utilised in infection with bacteria of the typhoid-paratyphoid-dysentery groups.

The specific disinfecting property of drugs is nevertheless of great importance from the standpoint of investigation into the chemotherapy of bacterial diseases. In addition there is the possibility of finding some substance which may possess sufficiently strong selective action in certain diseases of bacterial origin so that they may be useful in the internal disinfection of the tissues.

The following substances among others have been used in bacterial infection and will be described in some detail.

- (1) Aniline dye compounds. (2) Hydrocupreine derivatives.
- (3) Phenols and their derivatives. (4) Metallic and other compounds.
- (5) Chaulmoogra oil and its derivatives (see chapter on leprosy).

Phenyl methane dyes. The basic dyes of this group such as gentian violet, crystal and methyl violet have a selective lethal action on Gram-positive bacteria and much less for the Gram-negative organisms. They have a low toxicity for tissues and penetrate them readily. They have been tried in cases of staphylococcus infection both locally and intravenously.

Gentian violet is said to be harmless to the tissues and is bactericidal especially against staphylococcal infection. A local application in strength of 1 in 10,000 to 1 in 500 has been found useful. Young and Hill (1924) obtained good results with intravenous injection of the drug in septicæmia, chronic cystitis, etc. It is, however, a slowly acting germicide and leaves the blood stream very rapidly so that a minute or two after the injection the blood is no longer bactericidal. It would, therefore, be impossible to maintain in the circulation a bactericidal concentration for sufficient time to kill the microbes. Brilliant green another of these compounds, has been shown to possess high bactericidal property. Browning (1918) found this substance to be lethal to *Staphylococcus aureus* in dilution of 1 in 10,000,000 but the action is reduced in the presence of organic matter. Kligler (1910) showed that brilliant green killed *B. subtilis* and *Staphylococcus aureus* in dilutions of 1 in 15,000,000 and 1 in 4,000,000 respectively, while a concentration of 1 in 600,000 was necessary to kill *Bact. coli*; the dysentery group of organisms was killed in dilution of 1 in 1,500,000. Acid and basic fuchsin have also been tried and are said to possess high bactericidal power.

Acridine dyes. Acridine was introduced by Ehrlich in 1912 as a trypanocide under the name of trypanflavine; it is now known as acriflavine. Many acridine dyes have since been studied but only acriflavine and proflavine are actively antiseptic even in the presence of

wound-secretions. Although in many cases beneficial results have been obtained, there are many instances in which these dyes have proved ineffective. Acriflavine has been tried, like other dyes in influenzal pneumonia, urethritis, pyelitis, etc., but the results have not been encouraging.

Investigations have also been carried out on the bactericidal property of certain alkoxy derivatives of diamino-acridines. The most widely used of these compounds is rivanol which has been tried in the treatment of amoebic dysentery. The results of experiments with many of these compounds on streptococci *in vitro* are given below (Pindlay) :—

Compound.	Highest bactericidal dilution.
2-methoxy-9-ethanolamino acridine	... 1 in 60,000
2-ethoxy-9-ethanolamino acridine	... 1 in 80,000
2-allyloxy-9-ethanolamino acridine	... 1 in 100,000
2-propyloxy-9-ethanolamino acridine	... 1 in 40,000
2-isobutyloxy-9-ethanolamino acridine	... 1 in 40,000
2-isoamyloxy-9-ethanolamino acridine	... 1 in 16,000

Although many of these dye-stuffs have been shown to possess high bactericidal activity they have not been found effective in the treatment of diseases. Some of them produce toxic symptoms when given internally, while others are rendered inert in the body by combination with the proteins of the blood.

Hydrocupreine derivatives. The alkyl derivatives of hydrocupreine have been found to possess high bactericidal efficiency. The germicidal property of these compounds varies for different types of bacteria. Ethyl hydrocupreine is lethal to pneumococci while the higher derivatives such as eucupreine and vuzine are toxic to pus-forming organisms.

Experiments with optochin have shown that it is beneficial in pneumococcal infections. *In vitro* the drug inhibits the growth of pneumococci in concentration of 1 in 800,000 in serum; it kills them in 1 in 400,000 solution. The clinical efficiency in pneumonia in man however has been far less encouraging. Some clinicians have reported improvement if the drug is given in the first two or three days of the disease. Its application is limited by the fact that therapeutic doses are liable to produce toxic amblyopia.

Various other cinchona derivatives have also been tested for their bactericidal effect, and some of these compounds possess high bactericidal action *in vitro* but their action *in vivo* is feeble.

Phenol and its derivatives. Phenol is a general protoplasmic poison and a fairly active disinfectant. It precipitates proteins, but

the combination is so loose that it is split up allowing the compound to penetrate deeply into the tissue or into the body of the micro-organism. The bactericidal action of phenol depends upon its solubility in lipoids and proteins. Any condition which diminishes its solubility greatly interferes with the antiseptic property, hence alcohol or alkalies inactivate the effect of phenol. It has been shown that phenol kills *Bact. typhosum* in a few seconds at a concentration of 14 parts per 1,000, but dilution diminishes its bactericidal effect. Tubercle bacilli are killed by exposure to 5 per cent. solution for twenty-four hours.

By the introduction of an alkyl group into phenol, a series of compounds are produced which have great germicidal power. The most important of these derivatives are the cresols. The three isomers ortho-, para-, and meta-cresol differ in their bactericidal property, the meta- possessing the highest germicidal power being at the same time the least toxic; para- is the most toxic of all.

It has been found that among the various cresols, lysol, cyllin, izal, etc., have rapid bactericidal action in strong concentration, but they lose their activity in dilution. Chick and Martin (1908) showed that disinfectants of this class were ten times more bactericidal than phenol but quickly lost their activity in the presence of organic matter. The germicidal activity of these compounds is measured by determining the phenol co-efficient, that is, the ratio of the germicidal power of the disinfectant to the germicidal power of phenol, both being tested under identical conditions.

Caius and others (1927) studied the bactericidal action on *Past. pestis* of some commoner phenols and their derivatives *in vitro*. They found that introduction of the hydroxyl group into the benzene nucleus with the formation of phenol, greatly increases the antiseptic properties. The introduction of alkyl groups into the nucleus further augments the bactericidal power as shown by the three isomeric cresols which are better antiseptics than phenol. Solution in alkali either depresses or intensifies the effect of monohydric alcohols; the bactericidal power of thymol is depressed while that of carvacrol is intensified. In the case of the polyhydric alcohols, the bactericidal power is intensified in alkaline solution.

Etherification lowers the antiseptic value of dihydric phenols and the entrance of a propenyl radical, whether allyl (eugenol) or isoallyl (isoeugenol) in the molecule of guaiacol, enhances the bactericidal power. Among the substituted phenols the entrance of chlorine or bromine into the nucleus of phenol causes an increase in bactericidal power, as 2: 4: 6-trichlorophenol is sixteen times more powerful than phenol. The entrance of an amino group increases the bactericidal power.

In the case of the phenol derivatives, the nitroso derivatives act more slowly than resorcinol, the mononitro derivative is three times as active as resorcinol, while di- and tri-nitro derivatives are less powerful;

the entrance of the amino radicle increases the bactericidal power. The entrance of the nitroso radicle into the molecule of beta-naphthol increases the bactericidal power to sixteen times. Alkylation, halogenation and esterification augment the bactericidal power of phenolphthalein. Nitration increases the bactericidal power of fluorescein and its derivatives.

Though many of the phenol derivatives are good germicides and have been used for disinfection purposes and as antiseptic lotions for wounds and ulcers, internal disinfection with them has been a failure. Moreover they are markedly toxic when given internally.

Metals and their compounds. All heavy metals in high dilutions inhibit the growth of bacteria. It has been shown that 1 in 100,000,000 of copper in distilled water kills algæ. The colloidal metals in which the metallic particles are in an extremely fine state of division are physiologically inert; the only action which they can produce is by a small number of ions and this is inappreciable. Their therapeutic value in the treatment of bacterial diseases is very doubtful.

Most of the metallic salts have bactericidal properties in very high dilutions, dilutions such as would occur in the body after their administration in therapeutic doses. Copper sulphate kills *Bact. typhosum* in two hours in dilutions of one in a million in distilled water; mercuric chloride destroys the same organism in the same dilution in 24 hours. Many other metallic salts act in the same way. Unfortunately this action is very greatly weakened in the presence of electrolytes, and organic matter still further reduces this action. Their value in destroying bacteria in the tissues is therefore very doubtful.

It may be mentioned here, however, that although heavy metals cannot destroy bacteria in high dilutions in the presence of electrolytes and organic matter, they inhibit the growth of bacteria in very high dilutions. For instance it has been shown that mercuric chloride inhibits the growth of bacteria in nutrient broth culture media in a dilution of one in a million due to the liberation of metallic ions. This is the only kind of action which may be expected to take place in the body after administration of these compounds, and it may not be of much value in the actual treatment of many bacterial diseases where rapidity of action is imperative. The utility of most of these compounds is at present almost entirely confined to external disinfection and antiseptics of the skin, mucous surfaces, wounds, etc.

A few organic compounds of mercury and arsenic have been used in bacterial infections.

Mercurochrome, an organic mercury compound, has been much used as a germicide for intravenous injection. It has been recommended in many microbic infections, the chief of which are staphylococcus, and *Bact. coli*, the quantity used being about 0.005 gm. per kilo. body weight which gives a concentration of about 1 in 15,000 in the circulation. Fleming (1931), however, showed that in de-leucocyted blood mercurio-

chrome in a concentration of 1 in 2,000 has no power of inhibiting the growth of staphylococci while with normal blood the drug has no antibacterial power itself, but on the contrary impairs the natural bactericidal power of blood.

Mercurochrome has no germicidal action in a concentration more than twice the maximum obtainable after an intravenous injection. For further information see the chapter on mercury in Part III.

Walbum (1921) found that animals could be protected against lethal doses of organisms or toxins in many cases by a series of intravenous or subcutaneous injections of salts of certain metals. This he attributed to a temporary increase in the antibody content of the blood. Though general confirmation of his results is lacking, certain striking facts have been established with regard to the chemotherapy of metal-salts in infections with bacteria. It has been found that the action of these metals depends on (1) the pathogenic agent and on the species of the host, *i.e.*, the same metals are not effective against all the pathogenic agents, and also the same metals do not act similarly in animals of different species, (2) dosage: there being an optimum range of dosage an increase beyond which fails to influence the various infections and intoxications, and even may accelerate death, although the amounts which lead to these harmful effects may not in themselves be toxic for the host; (3) the time of commencement of treatment; (4) the virulence of the infecting organism, since in certain circumstances an infection with highly virulent organisms may be more amenable to treatment than one with the same organism but of lower virulence; (5) the diet of the treated animals.

In addition it has also been shown that metal-salts, which are therapeutically inactive alone, may be effective when administered along with homologous vaccine or antiserum. Thus Walbum showed that neither the injection of manganese-salt by itself nor of a vaccine of killed 'rat' bacilli alone cured mice infected with these organisms, but a combination of the two was effective.

Organic arsenic preparations. The efficacy of organic arsenical preparations in spirochaetal diseases is recognised. Douglas and Colebrook (1916) showed that salvarsan had a considerable bactericidal power on the hæmolytic streptococcus. Allison (1928) used it successfully in puerperal sepsis. Colebrook (1928) found the organic arsenicals to be specific against hæmolytic streptococci. He showed that with novarsenobillon a sufficient concentration in the blood can be reached which is lethal to the hæmolytic streptococci.

The organic arsenicals can therefore act as germicides in the circulating blood and they are useful in this respect in streptococcal infection and in anthrax infections. See also section on arsenic and treatment of individual bacterial diseases.

Other bactericidal substances. The bactericidal properties of the halogens and their derivatives are well known. A number of compounds

of chlorine are commonly used for disinfection of body tissues, *e.g.*, *eusol*, Dakin's solution, chloramine-T, dichloramine-T, etc. The action of these compounds is due to chlorine which occurs in them in a state of loose combination so that it is rapidly given up in the presence of proteins. The chlorine thus liberated combines with all forms of other proteins, including those of bacteria and in this way kills them. The disadvantage of these compounds is that when excess of other proteins is present, the chlorine combines with them and ceases to act as a bactericide. Chloramine compounds are more stable and give up their chlorine more slowly than compounds like *eusol*. They have therefore better disinfectant and antiseptic properties in contact with the body tissues. Compounds of iodine act in very much the same way.

Hydrogen peroxide and potassium permanganate owe their action to liberation of nascent oxygen. They readily decompose when brought in contact with the body tissues. Formaldehyde has a powerful destructive action on bacteria but is equally destructive to the tissues.

Conclusion. A perusal of what has been said above will show that, although we have many compounds which have a marked destructive action on bacteria and which are even effective in the treatment of external lesions produced by bacteria, the problem of obtaining substances which will produce internal disinfection and antisepsis still remains to be solved. Further research with such substances as aniline dyes, which have more marked bacteriotropic and less organotropic properties, is being carried out. It is hoped that compounds may be discovered in the near future which will destroy bacteria in the body tissues in the same way as therapeutic agents now destroy protozoa in the tissues. Till such compounds are discovered the specific treatment of bacterial diseases must be mainly with vaccines and sera, which only play a secondary part.

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CHAPTER II

SPECIFIC IMMUNE THERAPY IN BACTERIAL AND VIRUS DISEASES

In the prophylaxis and treatment of a large number of bacterial and virus diseases specific immune therapy has been extensively employed. This therapy consists of two measures, one having for its object the specific stimulation of the natural immunity mechanism of the body through the inoculation of a suitable suspension of the causative agent of the disease, *vaccine therapy*, and the other aiming at the destruction of the infecting organism or the neutralisation of its toxins, through the inoculation of ready-made specific substances or antibodies which are present in the sera of immunised animals, *serum therapy*. These two measures are suited for different types of diseases and when appropriately used they produce favourable therapeutic results. Serum therapy has been found invaluable in certain acute infections, where a rapid neutralisation of the poison is indicated and where it is desired to aid the overtaxed immunity mechanism of the patient. Vaccine therapy on the other hand has been of great benefit in prophylaxis and in treatment of a number of chronic localised infections, where the patient is not too ill and his immunity mechanism is not exhausted. But unfortunately at the present time, because of the growing tendency to apply these remedies in all sorts of unsuitable conditions, both forms of specific immune therapy in general and vaccine therapy in particular, have fallen into disrepute. In many instances the practitioner employs vaccine therapy not because he considers it suitable but because other remedies have failed and he cannot think of anything better. The common excuse is that "if vaccines do no good, at least they do no harm." This appears illogical, as we believe that any remedy that has potentialities for doing good also possesses the power to do harm, if improperly used. The unscientific attitude, the commercial exploitation of vaccine therapy, and

the utter disregard of the results which observation and experiment have made available, are to be greatly deprecated. The improper application of the therapy will only retard the progress of science and will help neither patient nor practitioner. It is the clear duty of the medical practitioner, by study and knowledge of the latest advances in immunology and bacteriology, and through the proper and scientific application of these valuable therapeutic agents, to contribute towards the progress of science and thus to the ultimate well-being of the community.

VACCINE THERAPY

The word vaccine is from the latin *vacca*, a cow. Cow-pox was called *vaccinia* or cow-disease and Jenner designated protective inoculation against small-pox with cow-pox virus as *vaccination*. Pasteur adhered to Jenner's nomenclature and applied the term *vaccine* to the suspensions of attenuated and killed bacteria that he used for immunisation. At present the term *vaccine* may be defined as a killed and enumerated suspension of organisms or their products, which when inoculated into the body, stimulates the tissues to produce antibodies which directly or indirectly bring about the destruction of the invading organisms and the neutralisation of the poison that the organisms may have produced.

Vaccine therapy has been in practice for a considerable length of time. In ancient China and India, the people had observed that one attack of small-pox protected them from subsequent attacks. They put this observation to practical use by exposing their children to mild cases of small-pox in order that a mild infection might be acquired and a lasting immunity secured. This practice was, of course, crude and attended by grave risks as it sometimes resulted in virulent infection and death. Many centuries later, Edward Jenner, as a result of his own observations and experiments, proved that cow-pox virus when inoculated into human beings produced a trivial infection followed by an absolute immunity against small-pox. Although he could not explain the principle or mechanism involved in

the process of immunisation, he may be justly considered to have laid the foundations of prophylactic vaccination. After Jenner, came Pasteur who while working with the organism of chicken cholera found that by leaving virulent cultures of the organism at the laboratory temperature for some weeks they became innocuous to chickens and were capable, when inoculated, of producing immunity in them. These inoculated fowls proved resistant to a subsequent inoculation with virulent organisms. From this he conceived the idea that by attenuating virulent organisms, and inoculating them into animals immunity might be produced. He put his theory into practice in a number of other bacterial infections and obtained convincing results. He established the value of prophylactic vaccination beyond any doubt. Following upon Pasteur's discoveries, preventive inoculation began to be widely practised both in animals and in man. In all his vaccines, Pasteur used attenuated living virus. The use of such vaccine in human subjects was attended with a certain amount of risk.

Salmon and Smith (1884-86) were the first to show that injection of dead cultures of bacteria were capable of establishing immunity in animals. But it was not till the work of Haffkine, Pfeiffer, Kolle and Wright, several years later, that the modern method of prophylactic vaccination in man was well established. Wright and his colleagues advocated its use for curative purposes, and according to them the justification for curative vaccination lay in the fact 'that in many instances infections are localised and that, while the local capacities of resistance may have been lowered, the immunity mechanism in other parts of the body may not have been brought into play and that vaccines by stimulating these may flood the focus of infection with antibodies and phagocytes and overpower the causative agent.' The experience gained during the past fifty years has vindicated in a convincing manner the value of vaccine therapy both in the prophylaxis and cure of disease.

A considerable amount of controversy has taken place as to the comparative value of living attenuated vaccine and vaccines prepared from killed cultures. Considering that a

certain amount of risk is attended with the use of living organisms for this purpose, the general opinion is in favour of the use of vaccines prepared from killed cultures.

Preparation of vaccines. Since the inception of vaccine therapy various methods have been devised for the preparation of vaccines. The selection of strains for such a purpose is very important according to our recent knowledge on bacterial variation. It has been shown by Arkwright (1927) in regard to *Bact. typhosum*, that in cultures there appeared colonies which had a 'rough' appearance while the normal colony was 'smooth' and shiny. These terms are now expressed by the letters 'R' and 'S,' the 'S' type is usually the normal pathogenic form, 'R' being the degenerate avirulent modification. 'R' variants are useless as protective vaccines. In view of this it is essential that in the preparation of vaccines 'R' variants should be rigidly excluded.

In addition to this, another type of variation, which is known as 'H' and 'O' variations of the organisms, has great significance from the point of view of immunity production. Smith and Reagh (1903) demonstrated the difference in the agglutination reactions between motile and non-motile forms of the same organism and later Weil and Felix (1916) working on the agglutination of *Proteus vulgaris*, differentiated two types of colonies in the culture ; the one is of a spreading type and the other discrete. The former is known as 'H' variant and the latter 'O' variant. It has been shown that the 'O' antigen of the smooth type of organisms is the one which is most important in the production of immunity and the 'H' antigen and the 'R' somatic antigen are of no protective value. In addition to these there is some other immunogenic antigen which is heat labile and it has been shown by Iyengar that over-heated vaccines of *Past. avisepticus* are inferior to vaccines heated to 60°C. or less.

The vaccines in common use are prepared in one of the three ways, depending upon the nature of the organism concerned; the ideal aimed at in the preparation is to render the organisms innocuous and to modify its antigenic structure as little as possible.

1. The ordinary vaccine is a suspension of killed organisms in normal salt solution. The organism is first isolated in a pure state by using a suitable culture medium. To an 18 to 24 hour culture of the organism normal saline is added and a uniform suspension of the organism obtained. The organism in the suspension is then killed without altering its antigenic structure by minimum heat or by addition of antiseptic, such as phenol. The purity and sterility of the vaccine are tested and the number of organisms per c.cm. enumerated. Finally the suspension is brought down to the required strength by dilution with 0.5 per cent. carbolised saline.

2. In diseases like small-pox and rabies the causative agent (filtrable virus) cannot be grown in artificial culture media. Therefore to prepare vaccines of these viruses they are cultivated in the tissues of animals (on the shaved skin of the abdomen of healthy calves in the case of small-pox virus and in the brain of sheep in the case of rabies virus) and an emulsion of the infected tissues made and tested for purity bacteriologically. The preparation and standardisation of these vaccines require great care and technical skill and in some countries a license has to be obtained for preparing these and only well equipped laboratories of a first class nature are granted permission to manufacture them.

3. For the preparation of vaccines which consist of the exotoxin or endotoxin of organisms, as for example, Koch's tuberculin, diphtheria, tetanus and scarlet fever toxins, the organisms are grown in special fluid media and when the maximum degree of toxicity is reached the medium is filtered, the bacterium-free filtrate standardised and vaccine prepared from it.

Varieties of vaccines. 'Live' vaccines. As the name implies the organisms in this vaccine are alive and not dead. Theoretically the ideal form of vaccine is the 'live' vaccine, because there is experimental proof that it calls forth a maximum response of antibody. In the prevention of small-pox the marvellous results obtained are due partly to the fact that the vaccine used is a 'live' vaccine. Recently, Alcock has used 'live' vaccine in gonorrhoea, but his results are not encouraging. While there are advantages in using a 'live' vaccine, the procedure is attended with grave risks and, therefore, cannot be recommended as safe for employment in human cases, except in a few select instances.

Sensitised vaccines. These were originally introduced by Resredka, and are prepared by growing the organism in suitable media and then mixing it with the appropriate immune serum, allowing the specific antibodies to get absorbed on to the organism, centrifugalising the suspension and finally resuspending the sensitised organism in normal saline. The vaccine is really a sero-vaccine and has antibodies present in it along with the organism. By sensitising the organism, the therapeutic value of the vaccine is said to be enhanced because larger doses can be given and there is very little reaction after injection. The preparation of sensitised vaccine is not only difficult and expensive but it is also not possible for all organisms. It can be made only in those cases where a potent specific anti-serum is available. It is commonly used in streptococcal infections and is well tolerated even by patients suffering from acute and generalised infections.

Autogenous vaccines. These are vaccines prepared from the organism causing the infection in the patient. Here one is certain that the vaccine prepared is antigenically specific and will give rise to antibodies that will produce maximum good to the patient. Wherever possible autogenous vaccine made by a competent bacteriologist should be used.

The recent advances in our knowledge on the antigenic structure of organisms and their powers of variation fully justify this view. When laboratory facilities are available as in big cities there is no excuse whatsoever for not getting an autogenous vaccine made. The indiscriminate use of stock vaccine has contributed largely to the disrepute into which vaccine therapy has fallen in certain quarters. In cases such as gonococcal arthritis where the infecting organism is difficult to isolate by cultural methods the use of stock vaccines is justifiable.

Stock vaccine. This term is applied to vaccines prepared from cultures of organisms obtained not from the patient but from others who have previously suffered from similar infections. This vaccine is readily available at a cheap cost to the practitioner. The vaccines put up in the market by commercial firms are of this nature. The chief objection to their use is that one cannot be certain in every case that the organism in the vaccine is antigenically the same as the organism in the patient. In the case of organisms like *Bact. typhosum* and staphylococcus in which different strains exhibit serological homogeneity there may not be much difference between stock and autogenous vaccines, but in the case of streptococci, pneumococci, *Bact. coli* and *H. influenzae* it is best to avoid stock vaccines as far as possible. All prophylactic vaccines are, however, stock vaccines prepared from a large number of strains.

Polyvalent vaccine. This is a vaccine consisting of several strains of the same organism isolated from different cases. In the case of organisms like streptococci and *Bact. coli* in which several serological "strains" are known to exist, polyvalent vaccines should always be used. Even when autovaccines are prepared of these organisms, a number of colonies of the organism in the culture should be selected for use. For prophylactic purposes polyvalent vaccines prepared by reputed laboratories should alone be used.

Mixed vaccine. This term is applied to vaccines composed of two or more organisms. When mixed vaccines are inoculated antibodies are produced against the different antigens present. These vaccines are generally employed in chronic infections of the respiratory tract, in which one generally gets a number of different bacteria in culture and is not certain which one of these is causing the disease and is important from the point of view of vaccine therapy. While it may be advisable to incorporate into a vaccine all the pathogenic organisms isolated from a case, experience shows that it is best not to use too many species.

Detoxicated vaccine. In the preparation of this vaccine, an attempt is made to remove the endotoxin contained in bacteria, so that larger doses of the vaccine may be used without giving rise to severe reactions. This may be done by dissolving the organisms in alkali and then precipitating by acids. How far it is possible to separate the endotoxin from an organism without altering the nature of the antigen contained

in it cannot yet be ascertained. One is also not certain if the endotoxins are after all unnecessary ; they certainly stimulate antibody production and as such may be helpful in immunity. The only advantage in using detoxicated vaccines seems to be that large doses can be given without producing undesirable reactions, but this advantage will be negligible unless there is an assurance that the usefulness of the vaccine is not reduced.

Formolized vaccines have been used in cases where the culture of the organism produces a powerful toxin. It has been shown that toxins treated with formalin lose the toxic property but retain the antigenic property. This principle has been applied to whole cultures. Broth cultures or saline suspensions of organisms are incubated with 0.2 to 0.5 per cent. formalin which procedure kills the bacteria, and where exotoxin exists, converts it into a nonpoisonous toxoid but still retaining its antigenic properties. It has been used with great success in the case of Shiga's dysentery bacillus (Ramon and Dumas, 1925, Durmand, 1925).

Defatted vaccines. Douglas and Fleming (1921) claimed that a tryptic digest of acetone-extracted bacteria furnished a good antigen. Dreyer (1924) prepared tubercle vaccine by first boiling the organisms in formalin and then extracting them with acetone. He claimed to have cured tuberculosis in guinea-pigs with the use of such a vaccine. Clinical trial in man appeared to be favourable in the beginning, but later observation did not show any advantage of this type of vaccine over the ordinary vaccines.

Lipo-vaccines. In these the bacteria are suspended in an oily medium, so that the vaccine substance would be slowly absorbed and the antibody-producing stimulus would be prolonged, thus approaching more nearly the condition in an actual infection. The available evidence goes to show that these are less effective than the ordinary vaccine suspended in saline solution.

Vaccines killed by chemical substances. Vaccines killed with various chemicals such as ether, iodine, and sodium fluoride have been extensively used in France with the idea that these not only kill the vegetative forms of bacteria but also detoxicate them, but they have not found favour anywhere else.

Bacterial extracts, filtrates and digests. With the idea that antigen in solution can react immediately with the body cells thus enhancing the immunisation process such extracts have been used. Although these are antigenic there is as yet no evidence to show that they are superior or even equal to the simple bacterial vaccine.

Autolysates. Sometimes the breaking down process proceeds too far and the immunising power of the vaccine is lost. More work is needed in this direction before this type of vaccine can be advocated for general use. In this connection it may be stated that bacteriophage is really a combination of bacteriophage and vaccine.

Antiviruses. These were introduced by Besredka (1919-24) with the idea that filtrates of cultures which have stopped growing contain inhibitory substances to which he gave the name 'antivirus.' He claims that animals inoculated subcutaneously or intradermally or poulticed on their shaved skin with staphylococcal or streptococcal antiviruses are resistant to inoculation of virulent cultures introduced 24 to 48 hours later. But this has not been substantiated by other workers.

Standardization of bacterial vaccines. In India at the present time no control whatsoever is exercised over the production and sale of therapeutic substances. Vaccines are therefore being largely used by practitioners without any knowledge of their nature or efficacy. The relevant clauses from the regulations issued under the Therapeutic Substances Act are outlined below :—

"The proper name of any vaccine shall be the name of the micro-organism from which it is made, followed by the word 'vaccine' unless the relative Schedule otherwise provides or if there is no provision in the relative Schedule some other name is approved by the licensing authority, provided that in the case of the under-mentioned preparations the proper name of the vaccine may be as follows : *Anti-typhoid vaccine; anti-typhoid-paratyphoid vaccine (T.A.B.); anti-typhoid-paratyphoid-cholera vaccine (T.A.B.C.); anti-plague vaccine; anti-dysentery vaccine; whooping-cough vaccine.* Cultures used in the preparation of vaccines must, before being manipulated into a vaccine, be thoroughly tested for identity by the generally accepted tests applicable to the particular micro-organism. The permanent records which the licensee is required to keep shall include a record of the origin, properties and characteristics of the cultures."

"Vaccines may be issued either singly or combined in any proportion in the same container. In the case of combinations of vaccines a name for the combined vaccine may be submitted by the licensee to the licensing authority, and if approved may be used as the proper name of the vaccine."

"The label on the container shall indicate the composition of the vaccine by reference either : (a) to the number of micro-organisms per c.cm.; or (b) to the weight of dried substance of micro-organisms per c.cm.; or (c) to the number of micro-organisms or weight of dried substance of micro-organisms used in preparing 1 c.cm. of the finished product."

Methods of administration. Vaccines are administered by the following routes :—

Subcutaneous. This is the route commonly chosen. Vaccines are best given at a point where the tissues are loose. The popular site is the outer aspect of the arm about one-third of the distance down from the shoulder to the elbow. When large quantities have to be given as in antirabic treatment the sides of the abdomen may be preferable. In the case of localised lesions some believe that injection of the

vaccine near the lesion is more advantageous, but there is no evidence in support of it.

Intravenous. Vaccines are sometimes given intravenously for the purpose of eliciting marked reactions. In the treatment of arthritis, typhoid, coli and gonococcal vaccines have been given in this way. The beneficial results noticed appear to be due to the non-specific protein reaction that follows rather than to the route of administration.

Oral. There is experimental evidence to show that oral administration of killed cultures of bacteria and certain toxins and poisons, to mice and rabbits, results in the production of a certain degree of immunity. Vaccines have, therefore, been given by the oral route specially in little children and in patients who cannot overcome their antipathy to inoculations. Besredka's bilh-vaccines are prepared specially for oral administration. From the available evidence it is certain that the oral method is not preferable to the subcutaneous method; it is even doubtful if it is efficacious at all.

Intracutaneous. Small-pox vaccine is used in this way. The cleaned skin is scratched gently by a needle or lancet, care being taken not to draw blood and then the vaccine lymph is applied to the scarified part and allowed to dry. Some prefer to give bacterial vaccines also by this route, but the advantages claimed are of doubtful value.

Dosage. Dosage varies not only with the nature of the vaccine used but also with factors such as age of the patient, nature of the illness, toxicity of the organisms, sensitiveness of the tissue affected, route of administration and the purpose of administration. In young children, in acute illness, when sensitive tissue like the lungs or the brain are involved, when the selected route of administration is intravenous or the purpose for which it is used is for cure of illness, the dosage has necessarily to be small. On the other hand, in adults, in chronic illness of a localised character, when the route is subcutaneous or when the purpose is prophylaxis, a larger dose will not be harmful. The first dose is purely an experimental dose, and the subsequent doses must be controlled by the local, focal and general symptoms. The production of any marked reaction, either local or constitutional, after an injection may be considered a contraindication to any increase in dosage. The time interval is another important factor to be considered. As a rule, 3 to 5 days or 7 days' intervals between doses is given for chronic or subacute infections and 48 to 72 hours' intervals in acute cases, but there is no hard and fast rule and the reaction

of the patient is the best guide. When stock vaccines are used the dose may be two or three times as large as those of auto-genous vaccine and when used for prophylactic purposes they may be about five times the initial dose. For assessing the importance and value of the different factors discussed, experience alone is the chief guide.

Reaction following administration. Local, focal and general reactions may be noticed after vaccine administration. In prophylactic inoculation where a large dose of vaccine is given, local and general reactions are common. The first is characterised by pain, swelling, redness and heat at the site of inoculation, and the second by slight chill, rise of temperature to 100 or 101° F., nausea, and headache. These symptoms usually subside within 24 hours. In curative inoculation on the other hand neither of these two reactions is generally present specially if the dosage is carefully chosen. It is advisable, in the best interest of the patient, to avoid these constitutional disturbances. The initial dose being a trial one, there may occur some slight focal reaction, but this should not be allowed to recur. Focal reaction is of a mild nature and disappears spontaneously.

Therapeutic Uses

The most convincing results have been obtained by the use of vaccine for prophylactic purposes. There is little doubt about the efficacy of the preventive inoculation in small-pox, rabies, typhoid fever, and plague. As regards diseases such as diphtheria, scarlet fever, cholera, influenza and pneumonia, the results are encouraging. On the other hand the therapeutic use of vaccines has not been very successful so far, but lately they have been used more extensively with greater success on account of the better method of preparation due to the recent knowledge on immunity reactions in relation to the antigenic structure of organisms. The success depends not only on the proper preparation of vaccines but also on the proper choice of cases. Experience alone can overcome these difficulties, and for this reason it is best to consult a competent bacteriologist who can advise as regards the suitability of the case as well as about the preparation and administration of the vaccine. When

a course of an autogenous vaccine fails to produce the desired effect, attempts should be made to detect any fresh infection by some other organism or by a different serological type of the same organism. In either case a fresh autogenous vaccine should be prepared incorporating the new organism. Sometimes it is difficult to isolate any organism from an infective focus or those isolated are of no use as vaccines. In these cases, the best results are obtained with stock vaccines. The advantages of autogenous and stock vaccines have already been discussed.

In some cases it is not enough to stimulate the defence mechanism of the body by vaccines alone but steps should be taken to ensure phagocytosis and the access of antibodies to the foci of infection. For example in the case of chronic abscesses vaccines by themselves will do no good unless the abscess is opened and evacuated as well. Where the useful co-operation of an experienced bacteriologist is not available the general practitioner should in the best interest of his patient keep himself in touch with the latest advances in vaccine therapy. It cannot be overemphasized that a properly prepared vaccine should be considered as a potent substance capable of causing much harm to the patient when wrongly used. Before the administration of a vaccine all these points should be carefully considered. In competent hands results are very encouraging in cases of localised infections and evidence is gradually accumulating to show that vaccine may also do good in generalised infections as well.

A few words may be said about the value of different preparations of vaccines. The simple vaccine consisting of killed cultures suspended in saline is perhaps the best and gives the most consistent result. As regards the other modes of preparation it is very likely that the antigen is altered as a result of the elaborate process necessary for the preparation in addition to the risk of contamination. The ideal vaccine would be one in which all the useful antigenic components of the bacteria are in solution. This can be properly standardised and therefore allows the actual effective dose of the vaccine to be more accurately measured. The reduction of toxicity of certain

vaccines by means of chemicals such as formalin is being more generally practised now and should be of much value in future.

The following is a brief outline of the more important vaccines used either in prophylaxis or treatment of diseases.

Typhoid Vaccine. It is a mixed vaccine consisting of a carbolised saline suspension of three organisms, *Bact. typhosum* 1,000 millions, *Bact. paratyphosum A* 500 millions and *Bact. paratyphosum B* 500 millions per c.cm.

For prophylaxis it is given subcutaneously in two doses of 0.5 c.cm. and 1 c.cm. at an interval of 7 to 10 days. Some people prefer to give a third injection after 7 to 10 days. For children the dose is proportionately reduced according to age.

This vaccine has been used extensively in the British Army since 1909 with very good results. The immunity lasts for about a year, and revaccination with a single dose of 1 c.cm. should be done every year. Intravenous inoculation of typhoid vaccine has been tried recently with very encouraging results. The immunity is said to last longer in these cases but owing to the danger of protein shock this method is not recommended.

Oral administration of vaccine has been extensively used in South Africa. The vaccine is given as a suspension in teaspoonful doses, or it can be made into a pill. Three doses each of 45,000 million organisms combined with ox bile in keratine-coated pills can be given. The results of oral administration are however inconclusive.

In the treatment of typhoid fever vaccines have been used with success. An initial dose containing 100 million organisms is given subcutaneously and subsequently three to four days apart, increasing the dose gradually; if sensitized vaccine is used this should be given daily for four days in doses of 500 to 1,000 million organisms subcutaneously or 100 to 200 million intravenously. From the available evidence it appears that typhoid vaccine may favourably influence the course of the disease, but it has been argued that the same results can be obtained by giving any other bacterial vaccine, and that the action obtained is most probably non-specific in character.

Bacillary dysentery. Two types of organism are mainly concerned in this infection, *Bact. shigæ* and *Bact. flexneri*. *Bact. shigæ* is a very toxic organism producing an exotoxin whereas *Bact. flexneri* is relatively non-toxic. On account of the toxicity of the Shiga type various attempts have been made to reduce the toxicity of these strains for the preparation of vaccine. For this purpose Boehncke (1917) introduced a toxin and anti-toxin mixture, which he called 'Dysbakta.' For prophylaxis this was used by Bischoff (1918) in doses of 0.5, 1.0, and 1.5 c.cm. at five days' intervals with great success.

Recently, formalised vaccine (anacultures) have been used with success but it has not as yet been tried extensively enough to enable one to assess its real value in prophylaxis. Vaccination against dysentery with oral administration of Besredka's bilivaccine is recorded to have given good results but they are not so uniform as in the case of subcutaneous injection.

In the case of *Bact. flexneri*, the preparation of a vaccine is much less difficult as it is nontoxic. Except that the vaccine should contain all the representatives of various antigenic groups there is no other precaution necessary in the preparation of the vaccine. The usual prophylactic dose is 250, 500 and 500 millions at weekly intervals.

Treatment of bacillary dysentery by means of vaccines is used especially in chronic cases. Opinions as to the efficacy of vaccine in such condition are very divergent but Nolf (1919) and Acton and Knowles (1924) report favourable results with autogenous and stock vaccines.

In the beginning vaccines may be given subcutaneously or intracutaneously starting with small doses such as 10,000 to 1,000,000 organisms and increasing to as high as 5 to 10 million organisms. Some clinicians have reported striking results in chronic cases with intravenous doses every fourth or fifth day and gradually increased from 5 to 60 million organisms. It has also been tried in combination with 150 to 200 c.cm. of water per rectum by the drop method. Polyvalent vaccines have also been tried by the mouth. Doses recommended are 20 to 30 drops on the first day, 50 drops on the second day and 60 to 70 drops on the third day. Vaccines in the form of tablets have been prepared for use during epidemics. Each tablet contains 100,000 organisms and 5 or 6 tablets may be given daily dissolved in water or sodium chloride solution. The results of vaccine treatment have varied greatly in the hands of different observers.

Cholera vaccine. It is only used for prophylactic purposes. The vaccine consists of 24 hours culture of the cholera vibrio suspended in normal saline, killed by heat at 56°C. for half an hour and 0.5 per cent. phenol added as a preservative. Vaccines prepared in India contain 8,000 million organisms per c.cm. and the usual prophylactic doses are 0.5 c.cm. and 1 c.cm. at an interval of a week. A third dose of 1 c.cm. may be given but is thought to be unnecessary. Sometimes cholera vaccine is mixed with T. A. B. vaccine to produce immunity against all simultaneously. In emergency when two doses cannot be given, a single dose of 8,000 millions will give rise to sufficient protection.

In the prophylaxis of cholera, extensive observations were made in India by Russell. He found that in the comparative trial of cholera bilivaccine (oral) and the ordinary cholera vaccine (subcutaneous), both conferred a high degree of immunity. Russell expressed the opinion that the subcutaneous method was superior, and was able to show

that five days after a single subcutaneous dose of cholera vaccine the immunity was about as high as that present three days after a full course of the oral vaccine.

Plague vaccine. Statistical evidence from different countries shows that vaccination against plague reduces the incidence and case mortality markedly. Haffkine's vaccine is used extensively in India. It is prepared by growing *Past. pestis* in goat-meat-digest-broth at 25° to 30°C. for 2-6 weeks, then killed by heat for one hour at 60°C. and 0.5 per cent. phenol added as a preservative. Schutze claims to have got better results in animal experiments by using cultures grown at 37°C. Flu (1929) prepared a vaccine from a culture of *Past pestis* dissolved by bacteriophage and heated to 44°C. for 4 hours in the presence of 0.5 per cent. phenol and claims to have got very good results in animals. In view of the above experiments bacteriophage lysed vaccine and Schutze's vaccine are worthy of trial in human subjects.

Two doses of the vaccine are generally given for prophylaxis, the first dose being 2 c. cm. and the second 4 c. cm. The interval between injections is 10 days. The results obtained from the use of this vaccine are quite convincing. In one very well controlled study in Bombay, it was found that while the incidence in the unvaccinated was 8 per cent., in the vaccinated it was only 1.3 per cent. and as against a mortality rate of 4.7 per cent. in the first group the rate was only 0.4 per cent. in the second.

Lobar pneumonia. A considerable amount of work has been done in recent years on the value of vaccines in the prophylaxis and treatment of lobar pneumonia and workers are unanimous that administration of pneumococcal vaccine confers a high degree of immunity in susceptible animals. The immunity is type specific so that in the preparation of a prophylactic vaccine all the common types have to be included. According to the recent work of Griffith on the variability of the types of pneumococcus there is a possibility of change in types after repeated mass inoculation so that the vaccine has to be changed accordingly.

The administration of such a vaccine for prophylactic purposes has proved to be of great value in mining areas in Africa and in the Army where the death rate used to be very high before the use of such vaccines.

For prophylaxis, three doses are given subcutaneously at weekly intervals, each dose consisting of 1,000 millions of each of the most common types of pneumococci. Dubos and Avery (1931) isolated a highly specific enzyme from a bacillus capable of decomposing the specific polysaccharide of type III pneumococcus. Animal experiments showed that it is effective both as a prophylactic and therapeutic agent in an infection with type III pneumococcus, but no conclusive experiment has been done on human subjects. It has been observed that in an epidemic of lobar pneumonia there is often a change in the bacterial flora. Other

organisms such as hæmolytic streptococci, *H. influenza*, staphylococci and *Nisseria catarrhalis* are frequently found either in addition to or in the absence of pneumococci. It is therefore better to prepare a mixed vaccine for prophylaxis. It should be noted that there is a limit to the varieties of organisms which can be included in the vaccine. When a large variety of strains are included in the vaccine it may not be possible to give a sufficient number of each to produce immunizing response.

As regards the treatment of lobar pneumonia with vaccine it has been seen that if administered early it influences the course of the disease so that combined with the serum treatment it may be of great help. Minor pneumococcal infections such as the common cold with bronchitis, chronic sinusitis and other nasal inflammations if unattended with any other pathological condition, e.g., deviated nasal septum, polypus, etc., are benefited by the administration of a pneumococcal vaccine. Where possible, autogenous vaccine should be employed but stock vaccine is also of benefit. In this condition the initial dose is 10 million organisms increased every 3 or 4 days, up to 100 millions, after this it is increased by 100 millions at weekly intervals. For prevention of exacerbations monthly injections of 100 millions should be continued during the winter.

Whooping cough. Results have been very variable with the use of this vaccine in the past when the importance of freshly isolated cultures was not recognised, but with the use of fresh cultures the results will most probably be better in future.

The following is a schematic representation of dosage of the vaccine for prophylaxis in millions of *H. pertussis* (from Fleming and Petrie, 1934).

		1st dose.	2nd dose.	3rd dose.
Under 1 year	..	400	800	1,600
1 to 2 years	..	800	1,600	3,200
3 to 5 years		1,200	2,400	4,000
5 to 10 years	.	1,600	3,200	4,000
Over 10 years	..	2,000	4,000	4,000

For treatment mixed vaccines are better than vaccines consisting of only *H. pertussis*. A combination of 500 millions of *H. pertussis* with 250 millions of *H. influenza* and 20-100 millions of pneumococci per c.cm. is very suitable. This is given every day or every 2 days to a child of five or six years in doses of from 0.2 c.cm. to 1 c.cm. Cockshut claims to have got extremely good results by the use of doses, 4 to 10 times of those recommended.

Influenza. During the last influenza epidemic extensive trials were made on the efficacy of a mixed influenza vaccine consisting of *H. influenza* 500 to 1,000 millions per c.cm., pneumococcus 1,000 millions per c.cm. and streptococcus 100 millions per c.cm. The dose is 0.25, 0.5

and 1 c.cm. at an interval of 4 to 7 days. The results as reported are extremely conflicting. Immunity does not last more than three months.

Acute rheumatic fever. Vaccine treatment of this condition with hæmolytic streptococci has given favourable results especially in checking the recurrences which are so common in this condition. Collis and Sheldon (1932) used weekly doses commencing with 200,000 cocci followed by 500,000 and then continued as follows:—1, 2½, 5, 10, 15, 20 millions followed by a gradual increase by 10 millions till 100 millions have been given. They administered the vaccine intravenously with safety.

Chronic rheumatic conditions. These include various forms of non-specific arthritis, fibrositis, perineuritis, etc. Various attempts have been made to treat these cases with vaccines prepared from organisms isolated either from the site of the lesion or from a septic focus in the teeth, tonsils, nasal sinuses, genito-urinary or intestinal tracts. Although it is very difficult to correlate the finding of organisms from such septic foci and the occurrence of rheumatic conditions yet it has been seen that vaccines prepared from them are able to alleviate or cure the condition in a large number of cases. Vaccine treatment should be auxiliary to any radical measures necessary for the removal of an infected focus. Autogenous vaccines are better than stock vaccines in these cases but the vaccine should be prepared by an expert. A stock vaccine for such conditions should contain a large number of strains from the mouth, tonsils, intestine and genito-urinary tract isolated from rheumatic cases.

The Arthritis Committee of the British Medical Association (1933) recommends an initial dose of 20,000 to 50,000 organisms when a septic focus is suspected or half a million when no septic focus exists. The doses are gradually increased every five or six days and it is rarely that a case will require a dose of more than 10 millions.

Acne vulgaris. This condition is due to a mixed infection with the acne bacillus and the staphylococcus. Vaccines prepared from both these organisms have been found to be of benefit in such conditions. The treatment should be continued for a long time to get any good result. Autogenous or stock vaccines may be used. The stock vaccine should contain both types of organism.

For therapeutic purposes mixed staphylococcus and acne vaccines are used. The dose of staphylococcus is from 200 millions gradually worked up to 2,000 millions. Acne bacillus is best given in an initial dose of 5 millions followed at weekly intervals by doses of 7½ and 10 millions. If there is no improvement with these, the dose should be increased to 100 millions, and should be followed by increases of 100 or 200 millions up to 2,000 millions. As the acne bacillus is but slightly toxic and very seldom gives rise to general reactions these large doses can be given with safety. Sometimes it is mixed with intestinal streptococci especially in cases where there is a preponderance of streptococci in the intestine. The dose used is similar to that of the acne bacillus. This

treatment should, of course, be combined with suitable medicinal, dietetic or physical treatment and regular evacuation of the contents of acne pustules and removal of comedones.

Furunculosis. Staphylococcus vaccine was the first vaccine used for therapeutic purposes by Wright. Usually staphylococci isolated from boils are antigenically similar so that there is very little difference between the use of a stock vaccine and autogenous vaccine. Vaccine in the treatment of furunculosis serves two purposes. Not only does it cure the condition but it also prevents the recurrence of this condition anywhere else in the body.

Large doses are recommended for indolent boils to produce a focal reaction which is beneficial in such cases. The usual dose in a severe case is 100 to 2,000 millions of staphylococcus. In less severe cases 200 or 300 millions may be the initial dose, increased at intervals of 5 to 7 days up to 1,000 or 2,000 millions. Usually six to eight doses are sufficient to cure even very chronic cases. But, failing with this vaccine, streptococci isolated from faces or boils may be combined with this vaccine.

Recently, Gratia (1930) has used a vaccine in which staphylococci were dissolved by certain streptothrices and moulds. This he calls *mycolysates* which are very beneficial in chronic cases. Bacteriophage lysed vaccines are also in use but the results so far are indifferent. As a result of the recent isolation of a powerful exotoxin from staphylococci, it is being used in modified form (toxoid) for the treatment of boils. This toxoid is prepared by incubating the toxin with 0.3 per cent. formalin for 2 days and injecting subcutaneously commencing with a dose of 0.05 c.cm. and increasing the dose every five to seven days by 0.05 c.cm. Although still in the experimental stage, the results so far obtained are very encouraging.

Coliform infections. *Bact. coli* vaccines are used both for prophylactic and curative purposes. For prophylaxis they are used in patients suffering from coliform infections of the urinary tract preparatory to a major operation of the genito-urinary tract. Cases for such treatment should be carefully chosen as there may be acute symptoms of coli fever following an initial dose in cases where there is an obstruction to the outflow of urine. The doses recommended are 100, 500 and 1,000 millions at weekly intervals.

For therapeutic purposes these vaccines are used for cases of bacilluria and pyuria which are resistant to ordinary treatment and in which no exciting cause can be found.

The initial dose in children over 5 years should be 20 millions, increased at weekly intervals to 500 million organisms. In adults the initial dose is 25 millions, increased gradually at weekly intervals to 2,000 millions if there is no focal or general reaction. Acute infections due to late lactose fermenting coliform bacilli are also treated with such vaccines. The initial dose of 25 millions should be given about

5 days after the temperature has returned to normal, the dose being increased gradually to 500 or 600 millions at weekly intervals.

Ulcerative colitis. Recently, a special type of diplococcus has been isolated from ulcers in cases of ulcerative colitis and vaccines prepared from such organisms either alone or combined with an antibacterial serum have been found to be of great benefit (Bargen 1924). The treatment however should be combined with strict attention to diet and removal of septic foci. The vaccine is prepared by culturing the cocci in broth for 48 hours, adding 0.4 per cent. tricresol to the culture to sterilise it and the concentration adjusted to 2,000 millions per c.cm.

An initial dose of 200 millions is given and if it is not followed by any reaction the dose is increased every third day up to the maximum dose of 2,000 millions per c.cm. Sterile filtrates of cultures of the organism have also been used, the maximum dose being 1.15 c.cm. of such filtrate.

Gonococcal infections. The use of such a vaccine has been of the greatest value in cases of complications resulting from an infection with gonococci, but used with caution it can be helpful in all stages of gonorrhœa. In the early stage it reduces the duration of primary infection and diminishes the number and severity of the complications. It is used in complications such as arthritis, epididymitis, orchitis, etc. According to the recent work of Torrey, gonococci are composed of many antigenically varying members so that any vaccine to be of use should either be autogenous or should contain a large number of these strains.

Various different vaccines have been used for the treatment of such conditions but the most commonly used is the simple vaccine prepared from freshly isolated cultures grown on serum agar. Mixed vaccines have been used in some cases consisting of staphylococcus, streptococcus or diphtheroid bacillus along with polyvalent gonococcal vaccine.

Only small doses are tolerated, and it is best to avoid any reaction. The dose also depends on the severity of the illness. In acute complicated cases it is advisable to begin with 500,000 organisms and gradually work up to 10 millions. In chronic cases the initial dose should be small but the amount administered may rapidly be increased up to 500 millions or more so long as there is no reaction.

Asthma. True asthma is a result of hypersensitiveness to some foreign protein. There are, however, many cases in which this is associated with bacterial infection and it is in these cases that vaccine therapy has been found to be of considerable value by many workers. Either autogenous or stock vaccines can be used. For autogenous vaccine organisms such as *H. influenzae*, pneumococcus, streptococcus or *Bact. friedlander* are obtained from sputum culture. In a certain percentage of cases refractory to such vaccines, organisms isolated from the intestine, particularly enterococci, are incorporated in the vaccines with great benefit. In determining the sensitiveness to the

various organisms isolated either from the sputum or intestine, dermal reactions are of great help.

The initial dose should always be small in order to prevent the precipitation of an attack. The initial dose of streptococci, 0.1 to 0.5 million are used, increased by 0.1 million up to 1 million and further continued, where necessary, to as large a dose as can be tolerated by the patient.

If there is reaction with any dose, the next one is reduced and further increase in dosage should be made with great caution. Freeman advocates 0.5 c.cm. of adrenalin mixed with the vaccine to avoid reactions.

Smallpox. The vaccine used for prophylaxis is a living attenuated virus and of all prophylactic vaccinations this is perhaps the most useful. According to reliable authorities vaccination has very appreciably reduced the incidence and the mortality rate of smallpox.

The vaccine is available in this country only in certain government laboratories and municipal vaccine depots. It consists of a glycerine emulsion of scrapings of pustules from calves inoculated with the smallpox virus.

The technique of vaccination. The skin of the forearm or upper arm is cleaned with soap and hot water and dried with a clean towel (no antiseptic is used). Two drops of the vaccine lymph are placed on the site of inoculation and the part is gently scratched with a lancet over an area of half an inch by one-third of an inch, care being taken not to draw any blood. The excess of the lymph is allowed to dry on the skin.

Rabies. This vaccine has been found to be very successful for prophylaxis. The principle of vaccination in this case is the immunization of the affected person during the period of incubation which is fairly long.

The vaccine consists of a one per cent. emulsion of the brain of infected rabbits or sheep, which have died of fixed virus infection, in 0.5 per cent. carbolized saline solution. The treatment with this vaccine is rather severe and the course is prolonged; 5 c.cm. of the above vaccine is injected subcutaneously in the flanks daily for 14 days. Certain complications due to hypersensitiveness may follow. It is claimed that the use of this vaccine has reduced the mortality rate of rabies considerably.

Diphtheria. In the past no method was known of immunizing children against diphtheria but with the increase in our knowledge on immunity various methods have been adopted for immunizing children against this disease. Until recently, toxin anti-toxin mixtures were used for prophylactic purposes but it has been found that the presence of active toxin in such mixtures is liable to give rise to accidents owing to carelessness in the preparation, storage, etc.

The recommendations of the Ministry of Health for immunization should be followed. They recommend that immunization should be

preceded by a Schick test to exclude children who are already immune. Positive Schick reactors who have simultaneously been tested for hypersensitiveness to toxoid and found to be negative, should be immunized by subcutaneous injection of formol toxoid in doses of 1 c.cm. on three occasions with fortnightly intervals. Another Schick test should be done some months after immunization to ascertain the development of immunity. The most suitable age for such immunization is between one and three years as very few children are hypersensitive to toxoid at this age and it is given at a period when they are most liable to infection. Children below one year need not be immunized.

SERUM THERAPY

The practice of serum therapy, began with the remarkable discovery of von Behring and Kitasato (1890) who showed that the sera of animals that had received injections of tetanus and diphtheria toxins had the property of neutralising these toxins and could prevent their poisonous effects. Following upon their discovery, Pfeiffer (1894) demonstrated that cholera vibrios, when introduced into the peritoneal cavity of immunized guinea-pigs, were killed and lysed. These observations lent support to the view that the blood sera of immunized animals contained protective substances which on being transferred to infected animals would help the latter to overcome the infection. Later on, attempts were made to prepare antisera against various bacterial infections and they were tried in the cure and prophylaxis of the corresponding bacterial diseases.

Although it was hoped in the beginning that antisera of high therapeutic value could be prepared against various bacterial infections by immunizing animals, the experience of the past four decades has proved to the contrary. The reasons are not far to seek. There are various virus diseases, *viz.*, small-pox, chicken pox, measles, etc., where the pathogenic organisms have not been culturally isolated in suitable antigenic forms, while there are others, *viz.*, typhoid, cholera, etc., in which though pathogenic organisms can be isolated, they fail to produce antisera of any therapeutic value.

A careful study of the available data reveals that the value of antisera varies with the type of the serum (whether anti-

toxic or antibacterial) and the time of administration in the course of the disease. For prophylaxis the usefulness of antisera seems to be limited. The protection they afford is only for a short period (4 to 6 weeks) owing to the rapid elimination and disappearance of antibodies from the blood. As a therapeutic agent the use of antitoxins is extremely helpful, especially in diseases like diphtheria where the toxin circulating in the blood is directly neutralised by the antitoxin, provided it is given early and in adequate dosage.

On the other hand, antibacterial sera are not of as much prophylactic or therapeutic value as the antitoxic. This is because such sera act partly by the presence of specific bacteriolysins, precipitins, etc., and partly by the mobilisation of the nonspecific immunity mechanism. Hence a higher concentration of antibodies in the serum does not necessarily mean greater efficiency. Still the administration of potent antibacterial sera in the early stages of severe bacterial infections, such as, Felton's antipneumococcus serum in type I pneumonia, polyvalent antimeningococcus serum in cerebro-spinal meningitis, in most cases cuts short the course of the disease and prevents unfavourable complications. It may, hence, be concluded that although the sphere of usefulness of antibacterial sera is limited, they are of considerable therapeutic value in certain selected cases.

Types and preparation of antisera. The antisera in common use may be divided into three types:

(1) Antitoxic sera, (2) antibacterial sera, (3) antiviral sera.

The methods of preparation of these are different and may be described briefly as follows:—

Antitoxic sera. These are prepared by immunizing horses by repeated inoculations of formalised toxins (0.2 to 0.4 per cent. of formalin added to the crude toxic filtrate and incubated at 37°C for from 4 to 6 weeks). The serum is obtained from such animals and standardised in terms of antitoxic units as prescribed by the official control authorities such as the Permanent Commission of the Health Organisation of the League of Nations. Official control also exists in most of the countries to regulate the standard of purity and potency of therapeutic sera.

Unfortunately there is no such control in India. The important and frequently used antitoxic sera are tetanus antitoxin, the diphtheria antitoxin, antivenin, etc.

Antibacterial sera. These are prepared by immunizing horses or other suitable animals by repeated inoculations of organisms. The antigen in this case consists of a suspension in physiological saline of the bacterium either living or killed, which contains both bacterial protein and endotoxin. The serum of the immunised animals contains antibodies against both. According to our recent knowledge on the antigenic diversity in certain types of organism and the extreme specificity in the action of the antisera prepared from such antigens, great care is necessary in the proper choice of antigen in the preparation of these antisera. In the preparation of a polyvalent antiserum, the different type specific sera are prepared separately and then are mixed together. Although by this method there is some weakening of potency due to the ultimate dilution of each type, it has been found to be better than the simultaneous injection of a variety of antigen which results in a low titre of antibody. The titration of such sera is done by estimating the different antibodies, *e.g.*, agglutinins, tropins, complement fixing antibodies, etc. or by animal experiments. Examples of sera mainly antibacterial are the anti-streptococcal, anti-dysenteric, anti-pneumococcal, anti-meningococcal, anti-plague, etc.

Antiviral sera. In certain diseases like measles or poliomyelitis, the causative organism is not known and cannot be cultivated *in vitro*, but there is ample evidence to show that immune bodies appear in the blood during the course of such virus infections. These immune bodies can exert a prophylactic and some curative action. Recently, therefore, the sera of patients recovered from such infections have been used for prophylaxis and curative purposes with favourable results. Patients free from tuberculosis, syphilis, or other infectious diseases are selected for this purpose and 500 c.cm. of blood from an adult or 100 c.cm. of blood from a child are obtained under sterile conditions, the serum separated, filtered and preserved by addition of 0.5 per cent. carbolic acid or 0.39 per cent.

of tricrosol. If kept in an ice chest, they retain their potency for months. Such convalescent sera are used in measles and poliomyelitis. Recently, convalescent smallpox serum has been used with very promising results in cases of encephalitis following vaccination. It has also proved to be possible to immunize animals against virus infections and thereby to obtain a serum capable of influencing the course of the disease against which the animal has been immunized.

The concentration of sera. It has been found that the bulk of the antitoxin is associated with the pseudoglobulin fraction of the protein, whereas protective substances in antibacterial and antiviral sera are associated with the euglobulin fraction. The different proteins of the serum, the euglobulin, the pseudoglobulin and the albumin, have different degrees of solubility in neutral salts. By adding appropriate concentrations of ammonium or sodium sulphate to the serum or plasma, different serum protein fractions can be separated for the purpose of concentration and purification of the sera. The advantage of such concentration and purification is that considerably larger quantities can be administered without the risk of foreign protein shock.

Storage and deterioration of sera. Sera must be kept in the dark and in the cold. The potency of most sera is maintained for a period varying from a year to two years after which there is a decline in the number of units of antitoxin in it, and if due allowance is made for this deterioration, sera may be used which have been kept for long periods than the time limit on the labels.

Modes of administration. The choice of the route by which an antiserum should be administered is a very important consideration because upon it depends the rapidity of absorption of antitoxin or other antibodies. For prophylaxis where rapid absorption is not a necessity, antisera are usually administered subcutaneously. But the proper choice of route in the therapeutic use of an antiserum is of the greatest importance. There are various routes through which an antiserum may be administered of which the following are the most commonly chosen. Subcutaneous, intramuscular, intravenous, intrathecal,

and other less commonly used routes are intraperitoneal, intracisternal, intraventricular, oral or rectal. The best route to be adopted in a particular case depends on the nature of the illness and the type of the antiserum, the severity of the illness, the stage of the disease at which antiserum is being administered, the age of the patient, etc.

Subcutaneous. This is the route commonly used although it is neither the best nor the most effective; for prophylaxis it is used very commonly. For therapeutic purposes, particularly in severe toxæmic cases, where rapid neutralisation of toxins is desirable, it is worse than useless, because the antibodies inoculated are absorbed too slowly to attain quickly the necessary concentration in the blood. The belief that this route is safer than the intravenous route has not also been substantiated by experimental evidence.

Intramuscular. This route is preferable to the subcutaneous and should be more widely practised. When sera are given by this route antibodies are rapidly absorbed and reach a high concentration in the blood in a comparatively short time.

Intravenous. This is the best route for administration of antitoxin where the aim is to get a direct neutralisation of the toxins circulating in the blood. In acute and severe cases where toxæmia is great and delay dangerous, the initial doses of serum should be given intravenously as a routine procedure followed by intramuscular or subcutaneous injections for the subsequent doses. Experience has shown that this route is not generally more risky than others if the serum is given diluted with normal saline and at body temperature.

Intrathecal. This route is preferable in diseases such as cerebrospinal fever, tetanus and poliomyelitis where it is desired to obtain the highest concentration of antibodies in the focus of infection. A lumbar puncture is performed under local anaesthesia and an amount of cerebrospinal fluid equal to or slightly more than the amount of serum to be injected removed and the serum allowed to run into the theca by gravity or by injection with a syringe. The quantity of serum given at a time is generally 20 to 30 c.cm. for an adult.

Intraperitoneal. Platou (1923) used this route in severe cases of diphtheria in infants where it was difficult to obtain suitable veins for intravenous injection. It has also been recommended by other workers and is said to be safe and well tolerated by the patients, but it has not been used much on account of the apparent risk of trauma or sepsis.

Intracisternal. This route of administration of sera has been employed to a considerable extent lately, especially in America in the treatment of cerebrospinal fever (Goldman and Borwer, 1931). It appears to be free from danger but should not be undertaken without

previous practice on the cadaver. The route is particularly suitable in cases with spinal subarachnoid block.

Intraventricular. This method has not been much used and it is doubtful whether the results are encouraging. Neal prefers this route to the cisternal route in cases with spinal block. In young infants ventricular puncture is best performed through the anterior fontanelle and the method is particularly useful in infants with a patent anterior fontanelle.

Oral. Although it has been shown that certain antisera are capable of exerting their specific effects when given by the mouth, the oral route is unquestionably the least effective. If this route is chosen at all, as for example in young infants, the serum should be diluted and given on an empty stomach in repeated doses.

Rectal. This route, although equally ineffective, is sometimes chosen to avoid serum reactions and discomfort following repeated inoculations. The rectum is cleared by an enema, the serum diluted with normal saline, made up to about 4 to 5 oz., warmed to body temperature and given high up with the help of a catheter.

Reactions following administration of serum. Parenteral administration of a foreign protein is sometimes followed by certain reactions. These are usually of moderate severity and do not constitute any danger to life. The factors that bring about such unpleasant reactions are bound up in part with the serum, irrespective of the specific antibody it may contain and in part with the degree of sensitiveness to the foreign protein of the person receiving it. The following are the common reactions met with.

In most cases the injection of antiserum is followed by only slight reactions, such as local pain and tenderness accompanied by mild fever which passes off in 24 to 48 hours. In a small percentage of cases, however, more severe reactions may follow.

Protein shock. This is generally observed after intravenous injections of large quantities of serum and is ascribed to the effect of foreign protein introduced. The reaction sets in within 15 min. to an hour and is characterised by chill, dyspnoea, cyanosis, rise of temperature, followed later by a fall of temperature to normal or subnormal, profuse perspiration and rapid pulse. The symptoms generally pass off without any treatment, but when they persist an injection of adrenalin

0.5 c.cm. or atropine 1/120 gr. subcutaneously is all that is needed to restore the patient to normal.

Serum sickness. This complication is seen in some persons about 8 to 10 days and sometimes even earlier, after the injection of serum. It is characterised by urticarial rash, pruritus, pyrexia, swellings of joints and lymphatic glands, malaise, oedema and albuminuria. The incidence and severity of serum sickness increase with the age of the patient. The frequency of reaction is said to be less after intravenous than after intramuscular injections, and serum of some horses is particularly liable to produce these reactions. The reason for this is unknown. The reaction is rarely severe and needs only symptomatic treatment. Calcium lactate in 10 gr. doses 3 or 4 times a day is beneficial; antipruritic lotions such as calamine lotion with 1.0 per cent. carbolic acid relieve itching; aspirin 5 to 10 gr. by the mouth reduces pain and pyrexia. When it is intended to give large doses, it is inadvisable, in order to avoid these unpleasant complications, to use concentrated sera in preference to ordinary sera. The incidence of this condition has been considerably reduced since the introduction of concentrated sera.

Anaphylaxis. This is one of the dreaded dangers that often dissuades the practitioner from using serum or giving it by the intravenous route. Anaphylaxis has undoubtedly been the cause of some fatalities, but it should be realised that the likelihood of its occurrence is remote, its incidence according to Park (1928) being only 1 in 20,000 and fatality 1 in 50,000. It can be avoided if a little care is taken and the case is studied before injection.

Some persons are extremely sensitive to the administration of a serum. These may be divided into two groups.

(a) Carriers of an hereditary allergic factor, *e.g.*, horse asthmatics who react almost immediately following the administration of a dose of serum.

(b) Persons sensitized by previous injection of a serum. The risk of death from allergic shock is very slight. But the administration of serum intravenously to horse asthmatics is more dangerous than to persons previously sensitized to serum

Although there is no risk of death the symptoms are sometimes alarming, characterised by a sudden onset, about a quarter of an hour after the introduction of the serum with restlessness, anxious expression, pallor, perspiration, rapid feeble pulse, deep and laboured respiration followed by cyanosis, unconsciousness, muscular twitchings, rigors, convulsions and involuntary micturition and defæcation. For this reason it is necessary to test the sensitiveness of a patient by intracutaneous injections of 0.05 c.cm. of 1 in 10 diluted serum. If after 10 to 20 minutes the resulting wheal increases in size and shows a zone of erythema the reaction should be considered positive. The degree of sensitivity depends on the extent of the wheal and reactions with pseudopodial projections are indicative of an extreme degree of sensitiveness. In America the conjunctival test is preferred to the intracutaneous test. It is said to be a more sensitive test but unfortunately is associated with the risk of damaging the cornea in hypersensitive subjects.

In such cases desensitization has to be carried on to allow introduction of serum in large quantities. This can be effected by (1) partition of the dose, and (2) slow administration of the serum.

In sensitive persons 0.01 c.cm. of serum is given subcutaneously and this dose is doubled every thirty minutes till 1 c.cm. in all is given. After half an hour 0.1 c.cm. is given intravenously and then doubled every 20 minutes till the full dose is administered. If there are any allergic symptoms at any time, the previous dose should be repeated instead of increasing the dose further. Administration of the serum may be preceded by an injection of 1/150 to 1/100 gr. atropine and adrenaline chloride solution (1 in 1,000) is kept ready for emergency purposes in case it is needed. The serum is given very slowly warmed and diluted to body temperature. When anaphylaxis comes on in spite of due care, symptomatic treatment should be given. Injections of adrenalin, pituitrin and atropine are useful. Inhalations of amyl nitrite or inhalations of oxygen may help.

Febrile reactions after intravenous injections of serum.
The reaction occurs about an hour after the intravenous dose and

is characterised by rigor, increase in cyanosis in pneumonia cases, profuse sweating and a fall in temperature. It is not a serious complication. Care should be taken to use sterile distilled water for the preparation of normal saline necessary for diluting the serum.

Neurological complications of serum treatment. Although they are rarely met with, the presence of these complications has been recognised lately. They may be classified into four groups (Allen, 1931). (1) A radicular type, resembling an Erb-Duchenne paralysis of acute onset; (2) a neuritic type, in which single nerve trunks are affected; (3) a polyneuritic type in which the clinical condition resembles that of a toxic polyncuritis; (4) a cerebral type in which the prominent features are probably referable to intracranial α -dema.

The condition has most often followed the use of tetanus antitoxin and the symptoms have appeared a few days after an attack of serum sickness. The patient complains of intermittent stabbing pains in one or more segmental areas or in the distribution of a peripheral nerve. Muscular weakness and wasting follow. This condition may persist for months but prognosis in such cases is generally good.

Dosage of antisera. The dose is dependent on so many factors that there cannot be any generalisation in the question of dosage. It depends on the type of serum, the severity of the disease, the period at which it is administered and the age of the patient. Each case is judged on its own merits; dosage has been discussed when dealing with the different antisera.

Antitoxic and Antibacterial Sera

Diphtheria antitoxin. This is obtained by immunising horses against diphtheria toxin. Only the exotoxin is used for immunising purposes. Such a serum is capable of directly neutralising the diphtheria toxin.

There cannot be any universally accepted scheme of dosage as in various diseases the interval elapsing between the onset of the disease and the time of administration of the serum have all to be considered. The following two tables of dosage given by experienced authorities are perhaps the best guide to a system of dosage which adequately represents our scientific knowledge and clinical experience.

The following table modified from Park and Williams (1934) gives the units of antitoxin to be administered to cases of varying grades of severity.

		Route	Dosage	
			Children weighing up to 50 lbs. (under 15 years of age)	Children and adults weighing 50 lbs. and over.
Mild	cases	Intramuscular.	3,000—5,000 units	5,000-10,000 units
Moderate	,,	,,	5,000—10,000 ,,	10,000-15,000 ,,
Severe	,,	Intravenous* or intramuscular and intravenous.	10,000- 20,000 ,,	20,000- 0,000 ,,
Malignant	,,	Intravenous*	15,000—30,000 ,,	30,000-60,000 ,,

*When given intravenously one-half the amounts stated.

Cases of laryngeal diphtheria, moderate cases seen late at the time of the first injection, and cases of diphtheria occurring as a complication of the exanthemata should be classified and treated as 'severe' cases. In all cases a single dose of the proper amount, as indicated in the schedule, is recommended, or the following simple table of doses may be adopted.

Doses recommended are :—

		Mild	Moderate	Severe	Malignant
Children	...	4	8	16	32
Older	..	8	16	32	64
Route	..	IM	IM	IV	IV

(IM—intramuscular, IV—intravenous; the numbers refer to thousands of units of anti-toxin).

These are rough guiding doses and each case must be considered on its merits. The earlier the injection the more certain and rapid the effect—one large dose given early is far more efficacious than divided doses. It is easy to give too little but it is very difficult to give too much.

The mode of administration is of great importance, as the object in antitoxin treatment is to attain an effective concentration in the blood with the least possible delay. The ideal method therefore is the intravenous for all cases and the next best is intramuscular in which the rate of absorption is 3 to 6 times greater than the subcutaneous. Platon (1923) suggested the intraperitoneal route in cases where it is

difficult to find the veins particularly in infants and children. This route has not been chosen to any extent perhaps on account of the risk of trauma or sepsis. It is important to mention here the fact that the efficacy of antitoxin is greatest when given early in the attack and that it decreases as the day of administration is delayed.

Tetanus antitoxin. This antitoxin is capable of neutralising free toxin in the system but is ineffective against toxin fixed in the tissues. Therefore it is of the greatest value in prophylaxis and the therapeutic use of such a serum is necessarily very limited. The prophylactic use of such a serum not only prevents the occurrence of the disease but also influences the character and progress of the disease in patients who subsequently develop it, increases the period of incubation and the incidence of local tetanus, thus lowering the rate of mortality.

For prophylaxis, the amount to be injected depends on the severity and the degree of contamination of the wound as well as the interval that has elapsed since its infliction. 1,000 to 3,000 international units (500 to 1500 U.S.A. units) are given intramuscularly before any attempt to clean the wound by surgical methods is made. Ramon and Loeller (1927) recommended the following procedure: 10 c.cm. of antitoxin and 1 c.cm. of anatoxine (anatoxic formolised preparation) are administered at different places. Antitoxin is repeated ten days later and after another ten days 2 c. cm. of anatoxine is given. This method is said to afford protection in those patients who have incurred a risk of tetanus.

It is of much less value in the treatment of tetanus but there is general agreement that the system should be flooded with tetanus antitoxin at the earliest manifestation of tetanus. The following scheme of dosage recommended by the War Office Committee 1917 may be usefully followed:—

Day of disease	No. of international units to be given by		
	Subcutaneous route	Intramuscular route	Intrathecal route
1st day	...	16,000	32,000
2nd day	...	16,000	32,000
3rd day	...	8,000	...
4th day	...	8,000	...
5th day	4,000
7th day	4,000
9th day	4,000

Antistreptococcus serum. This serum is very extensively used now-a-days for the various infections associated with *Streptococcus hæmolyticus*. It is used in scarlet fever, erysipelas, puerperal sepsis, endocarditis, cellulitis and surgical infections. The value of its use in these various conditions is very difficult to assess. But from the available data it can be safely concluded that it undoubtedly influences the course and complications of the disease. It also favourably influences puerperal

infection and acute inflammatory and septic conditions when they are known to be associated with a hæmolytic streptococcus.

The serum is usually given by the intramuscular route in doses of from 10 to 50 c.cm. of a concentrated preparation, the amount varying according to the age of the patient and severity of the symptoms. To be of any use, it should be given within 4 days from the onset of the disease, with concentrated sera the reactions are less marked.

Antidysentery serum. The chief bacterial species calling for serum treatment in the order of their importance are the following:—*Bact. shiga*, and *Bact. flexner*. Although there is some divergence of opinion on the efficacy of antidysentery serum, there is considerable evidence of a general nature to support its use. The best results are obtained with the Shiga serum, but the results are quite satisfactory with the use of Flexner serum also. In the preparation of antidysentery serum (Flexner) all the types of antigens such as V.W.X. (Y) and Z should be included in immunizing horses. The Flexner serum consists of antibacterial element only whereas the Shiga serum is antitoxic. Some people are of opinion that the efficacy of the serum increases if there is a sufficient amount of antibacterial component in addition to the antitoxin. Although Shiga serum can be standardised, there is no method available to standardise the Flexner serum.

Serum for therapeutic purposes should be given early (12 to 24 hours after the onset of symptoms) and in adequate dosage to get the best results. In cases where the nature of the dysentery has not been diagnosed it is best to use a polyvalent serum. In cases of ordinary severity a single injection may be followed by remarkable improvement, but in severer cases the dose has to be repeated in from 12 to 24 hours, and again in 48 hours. In Shiga infection 3,000 to 4,000 units should be given in mild cases and 5,000 to 10,000 in more severe cases. Serum in strength of 1,000 units per c.cm. is generally obtainable, but the more concentrated preparations contain about 5,000 units per c.cm. The early stages of the disease are undoubtedly benefited by large doses of the serum and the death rate is low, but after the first week of the disease it is less effective and of no value in chronic cases. In patients suffering from severe toxæmia the best results were obtained by intravenous injection of 60 to 80 c.cm. of the Shiga serum followed by 150 to 300 c.cm. of normal saline, administered twice daily for the first two days and once daily for the next two days. In very toxic cases 5 per cent. glucose in distilled water is substituted for the saline. In less severe cases the intramuscular route is preferable to the subcutaneous route, which is painful, and the dose should not be less than 40 c.cm. in an adult and as much as 100 c.cm. may be given.

High rectal injections of 10 to 30 c.cm. of polyvalent serum after cleansing the bowels with 1.5 per cent. sodium bicarbonate and followed by starch and tincture of opium have also been tried. Intramuscular injections should be given at the same time. The varying results given

by the serum are probably due to the difficulty in standardising and the varying qualities of sera on the market.

Antipneumococcus serum. Of late the use of antiserum in the treatment of lobar pneumonia has been given much prominence. Opinions are however divided as to the efficacy of serum in the treatment of pneumonia, but sufficient evidence is available to show that the mortality rate of type I infection is reduced significantly in serum-treated cases (Cecil and Plummer, Park, Bullowa and Rosenbliith), and specific serum therapy is less efficacious in type II pneumonia. Two types of sera are available for this purpose.

1. Huntoon's antibody solution which contains antibodies against types I, II and III. Although clinical results are satisfactory with this serum, it gives rise to severe febrile reactions on intravenous injection, and its use is not recommended.

2. Felton's serum is a concentrated serum containing antibodies against type I and type II pneumococcus. It is so titrated that one unit is contained in that amount of serum which is capable of neutralising one million lethal dose of a virulent pneumococcus culture.

The use of such a serum reduces the temperature, pulse rate, respiratory rate and the toxæmia. The inflammatory change in the lungs is checked, but it has no influence either on the rate of resolution or on the complications.

The intravenous route is the method of choice for the administration of the serum. If there is any reaction it can be controlled by intramuscular or intravenous injection of 0.5 to 1 c.cm. of 1 in 1,000 adrenalin solution. The risk of allergic reaction following the first dose may be minimized by slowly giving 1 c.cm. of serum intravenously either pure or diluted with sterile normal saline. The rest of the dose is given after an interval of 20 to 30 minutes.

There is no uniform scheme of dosage, the dose depending on the severity of the case, and the time of administration in the course of the disease. Cecil advises an initial dose of 5 c.cm. followed in one or two hours by 15 to 20 c.cm. of the serum and a dose every 2 or 3 hours thereafter till 100,000 units have been given (usually 100 c.cm.). The doses are halved if the patient shows signs of improvement. An additional dose of 10 to 20 c.cm. may be given on the following day.

Antimeningococcus serum. It has been used extensively in the treatment of cerebrospinal fever for a long time. The earlier reports as to the efficacy of such a serum were somewhat exaggerated, but the present day opinion is that the serum, given early, controls the infective process and shortens the illness. The complications and sequelæ are much less; relapses are also less frequent and the disease does not continue so long. Although this is the usual experience with antimeningococcus serum, there are some cases where this form of treatment fails entirely. The reason for this is that the meningococcus consists of a heterogenous antigenic group and the serum to be effective

must be prepared from a large number of representative strains from these different antigenic groups. Further it has been seen that strains isolated from sporadic cases are different from the epidemic strains and sera prepared from such strains are of little therapeutic value in epidemics. The best method therefore would be to collect a surplus stock of the serum during an epidemic period and to use it for the next epidemic till organisms are freshly isolated and fresh sera raised.

There is no known method of titrating this serum. The experiments of McKenzie and Martin have shown that substances bactericidal to the meningococcus are present in increasing amounts in the serum of acute and chronic cases of cerebrospinal fever and the serum of convalescents. Encouraging results have been reported on efficacy of such a serum in the treatment of cerebrospinal fever but technical difficulties have hindered its trial on a large scale.

Daily intrathecal injections of from 30 to 60 c.cm. for an adult and 10 to 20 c.cm. for infants have been found to give satisfactory results. At least 4 doses in all should be given, but there cannot be any hard and fast rule about the dosage since it depends on the severity of the illness and various other factors. Two points should be noted in its administration:—(a) It should be given as early as possible, (b) the amount administered should be less than the cerebrospinal fluid removed. The serum should be given warmed to the body temperature and by the gravity method. Two or three additional doses should be given after the disappearance of the cocci from the cerebrospinal fluid in order to safeguard against relapse.

As regards the route of administration, the intrathecal route is the best, but in predominantly bacteriæmic cases intramuscular injections of the serum may also be given in addition to the intrathecal injection. The intracisternal route is recommended in cases of sub-arachnoid block and is widely practised in the United States. It should not be undertaken by persons who have not had previous practice on cadavers.

Anti-anthrax serum. Anthrax is primarily a disease of animals and man is attacked only when engaged in an occupation which brings him in contact with such infected animals or their products. Of the three clinical forms of the disease the cutaneous type is the only one in which the administration of an antiserum is of some benefit. Although many different types of sera have been prepared and used from time to time, Selazo's serum, which is perhaps the earliest preparation (1895), is the best.

Selazo's serum is given in doses of 30 to 40 c.cm. subcutaneously followed by a similar dose after 24 hours if the local lesion or the general state of the patient does not improve. In severe cases 10 c.cm. should be given intravenously and repeated after 2 or 3 hours. In addition subcutaneous doses should be given as well. It should be noted that

the best results are obtained by the administrations of the serum at the earliest possible moment.

Antityphoid serum. Although attempts have been made to use antityphoid serum in the prophylaxis and cure of typhoid fever, the results have been very contradictory and the value of such treatment is extremely doubtful. Gross (1930) prepared a necrotizing toxin from *Bact. typhosum* and he used this toxin for immunizing horses. The antitoxin so prepared is capable of producing both a prophylactic and curative action in mice. Besides the antitoxin it also contains agglutinins, complement fixing and bactericidal bodies. Reports on the clinical use of such a serum will be of great interest.

Antivenin. This is an antitoxic serum against snake venom and considering the large number of deaths occurring in India from snake bite, it should be one of the most useful antisera. Unfortunately however there are so many practical difficulties in the preparation and use of this serum that it has not so far been very successful. For details see chapter on snake venom.

Antistaphylococcus serum. That the pathogenic staphylococci, particularly *Staphylococcus aureus*, may be associated with a toxin has been known for a long time, but the disaster at Bundaberg in Queensland in 1928, when 12 children died within 2 hours after being inoculated with a diphtheria prophylactic consisting of toxin-antitoxin mixture, which had become contaminated with staphylococci, led to renewed interest in the subject. Parker (1924) and Parker, Hopkins and Gunther (1926) recommended the growth of the staphylococci in an atmosphere containing 10 per cent. carbon dioxide and the use of Difco peptone instead of Witte's peptone for the production of the specific toxin in the culture medium. Gross (1929) has prepared an antiserum, which is both antitoxic and antibacterial. He prepared this by simultaneous injection of the toxic filtrate subcutaneously and heat-killed coccal suspensions intravenously. He titrates this antitoxin against a dry standard toxin by skin tests on rabbits. The standard toxin is taken to be that amount which when injected intracutaneously into rabbits causes a well-marked necrosis of the skin within 24 hours.

Puerperal infections caused by the staphylococcus have been treated with large daily doses (100 c.cm.) of this serum in Germany. It should be used as a precautionary measure in cases of furuncles of the lip, carbuncles, puerperal infections. The use of staphylococcal toxoid in the treatment of furunculosis has already been discussed in the section on vaccine therapy.

Antigasgangrene serum. The importance of this condition in the infection of wounds was recognised in the last War. Wounds grossly contaminated with soil containing anaerobic and aerobic organisms are most likely to show signs of gas gangrene. Antiserum prepared

against *Cl. welchii*, *Cl. oedematiens* and *Cl. novyi*, which are the commonest infective agents in such wounds, was extensively tried both for treatment and prophylaxis and has been found to be of great value particularly in prophylaxis. Gas gangrene is not so commonly met with in civil practice but in the likelihood of a wound being infected with anaerobic bacilli, a polyvalent antiserum should be injected as a prophylactic measure. The serum given intravenously and injected into the deep tissues near the wound has been found to give satisfactory results and as much as 1,000 c.cm. may be required. It is most important to treat the wound surgically in addition to the serum treatment.

This serum has also been used in acute abdominal conditions such as appendicitis and intestinal obstruction. Williams recommends administration of 80 c.cm. of the serum intramuscularly and an additional 40 c.cm. intravenously in very severe cases of intestinal obstruction. On subsequent days 40 to 80 c.cm. should be given intramuscularly until the distension has disappeared and the bowels are moving spontaneously and regularly. A prophylactic dose before operation is advisable. Its administration as an adjuvant to operative measures has proved to be of great benefit. It has also been used in the treatment and prophylaxis of puerperal sepsis due to infection with these pathogenic anaerobic organisms. For such infections Wrigley recommends the use of 40 c.cm. of the concentrated specific serum for prophylactic purposes. Other conditions in which this serum has been found to be useful are perirectal abscess, gangrene of the lung and diabetic gangrene.

Antiviral Sera

Measles. The cause of this disease is a filtrable virus which is present in the blood and nasopharyngeal secretions during the acute stage of the disease. It has not been possible to obtain an antiserum by immunizing animals so that human convalescent serum is needed for prophylaxis. This serum has no curative value. There are two types of protection:—(a) Full but temporary protection; (b) incomplete protection resulting in a mild attack of the disease. One attack of the disease confers a lasting immunity.

Full protection may be needed for children in a poor state of health, particularly those below three years, for children suffering from tuberculosis, rickets, diphtheria, whooping cough or scarlet fever if exposed to the risk of infection.

The effective dose for such a purpose depends on, (1) the age of the child; (2) the state of his health; and (3) the interval between the time of exposure to the infection and the time when the serum is given; this should not be more than five days. The average minimum dose is 1 c.cm. and the dose for children over three years of age is determined

by multiplying the age of the child by two and the result gives the number of c.cm. of serum to be administered. The duration of the protection so conferred depends on the time of its administration. If it is given before exposure the immunity lasts from 2 to 4 weeks, but if given early in the incubation period, some degree of active immunity may be superimposed upon the passive immunity and if this happens the patient will be protected for a few months.

Convalescent serum, normal adult human serum and whole adult blood are three different agents used for such protection. It is not always easy to obtain convalescent serum so that normal adult human serum from persons who had an attack of measles in their childhood may be used with the same result, but it has to be used in larger doses. The use of adult whole blood has the advantage that children can be injected with the blood from their parents when it will be unnecessary to perform a Wassermann test. The adequate dose of adult serum is 12 to 25 c.cm.; of the whole blood 25 to 50 c.cm. are needed to confer full protection.

Acute anterior poliomyelitis. Human sera from three sources are used:—(1) Convalescent serum; (2) serum from persons who had an attack previously even up to 10 or 20 years; (3) serum of normal adults with no history of having suffered from the disease. There is evidence to show that normal human serum contains immune bodies probably as a result of an acquired immunity due to sub-infective doses of the virus in childhood.

From 10 to 20 c.cm. is given at the earliest possible moment intrathecally, and this is followed immediately by a dose of from 40 to 200 c.cm. intravenously. The intrathecal dose may be repeated on two or three successive days, but there is no necessity for repeating the intravenous dose. There is no danger in injecting human serum intravenously, as it is rarely followed by unpleasant sequelæ. It is no use giving the serum after paralysis has set in.

Prophylactic inoculation can be done either by human antiviral serum or by immune serum from horses. Flexner and Stewart (1928) suggest a subcutaneous dose of 10 c.cm. for children and 20 c.cm. for adults repeated after 4 or 6 weeks if exposed to infection.

Chicken pox. Although a comparatively harmless disease, prophylactic measures are justified due to the long incubation period necessitating a prolonged quarantine. Convalescent serum has been used for this purpose.

Mumps. Convalescent serum has been used both for prophylaxis and alleviation of symptoms and complications of this disease. The results so far obtained are encouraging but not convincing.

Dengue. Convalescent serum has no protective action when given prophylactically or in the treatment of the disease.

BACTERIOPHAGE THERAPY

The discovery of bacteriophage is of comparatively recent date. Twort (1915) in a paper entitled "Investigation on the nature of ultra-microscopic viruses" first noted the existence of such an agent. d'Herelle, working at the Pasteur Institute, Paris, discovered a curious phenomenon in sterile filtrates of stools of patients suffering from the Shiga type of dysentery. The unique feature of this phenomenon, and one outside the realm of previous experience, was that the lysis produced by filtrates in cultures of this organism was transmissible in series *ad infinitum* without exhaustion of the lytic principle. This lytic principle was named *Bacteriophagium intestinale* or *Protobios bacteriophagus*. d'Herelle (1917) considered the bacteriophage to be a minute, ultra-microscopic, living organism, parasitic upon, and lytic towards bacteria and he has since done considerable amount of work in support of this theory.

Although bacteriophage, as we now know it, has been known for only 18 years, there are to be found indications of appreciations of its existence in the past. Most discoveries have their roots in the past. In certain parts of India the droppings of birds have been used for centuries past in the treatment of dysentery and other intestinal diseases; the use of cow-dung spread on the floors of kitchens as a purifying agent, was at one time, and still is, in many, if not all, parts of India, a common routine in the households. These practices were undoubtedly based on experience and clinical observations of many generations. The droppings of birds have been shown to contain very powerful bacteriophages against the organisms of dysentery, at times against the cholera vibrio, and even the typhoid group of organisms. The spreading of cow-dung to 'purify' the kitchen-floors, etc., although now shrouded in the rituals of religion, is an efficient, though undoubtedly a very primitive form of disseminating bacteriophage. The drinking of river waters, the administration of certain waters to the sick would also appear to be a method of bacteriophage prophylaxis and bacteriophage therapy.

Hankin (1896) drew attention to the purifying effects of the river water. He noted the bactericidal properties of the waters of the Jumna. At Agra, for instance, he found that the river water contained 100,000 bacteria per c.cm., whereas 10 miles further down there were only 100 per c.cm. This observation remained unexplained till the discovery of bacteriophage. Other workers also observed many peculiarities in cultures of intestinal organisms. Gildemeister (1917) observed the nibbled appearance and defective colonies of dysentery and coli organisms without recognising their abnormality. This we now know as a phenomenon of bacteriophage.

Nature of bacteriophage. Opinions differ regarding the nature of bacteriophage. A controversy as to whether it is a living organism or a dead product of a living organism is still raging. If we consider the size of bacteriophage it will be appreciated how very difficult it is to settle the question of the nature of such an object. Bacteriophage is ultra-microscopic, *i.e.*, not visible by the most powerful microscope. It has a dimension of 20 to 30 $\mu\mu$ *. Recent studies show that phages are composed of particles whose size is uniform for any phage, though varying from phage to phage. The smallest phage has a diameter of 8 to 12 $\mu\mu$, while that of the largest phage varies between 50 to 75 $\mu\mu$.

According to d'Herelle bacteriophage is an autonomous, living, strictly parasitic organism belonging to the group of filterable viruses, which multiplies at the expense of, and causes the dissolution of bacteria. He is of opinion that there is but one bacteriophage with an infinite number of strains. To this parasite he has given the name of *Protophobos bacteriophagus*. Other workers do not believe that bacteriophage is a living ultramicroscopic organism. Many consider that bacteriophage is a ferment, either living or dead. Kabesima (1920) considers it to be a secretion from the intestinal glands that acts as a catalyst on the proferment contained in all bacteria and causes their digestion. Bail (1921) formulated the hypothesis that bacteriophage is a disintegration product of bacteria, probably derived from the chromosomes. Bordet and Ciuca (1921) consider that the phenomenon of bacteriophage is due to an inherited autolytic power on the part of bacteria. Hadley (1928) is of opinion that bacteriophage, as it occurs, is a definite stage in the life cycle of all bacteria or that it is an essential constituent accessory to the various stages. Otto and Munter (1924) state that it is a ferment-like action of the colloidal particles of bacterial cytoplasm.

* $\mu\mu$ or millimicron— $1/1,000$ th μ , or $1/1,000,000$ mm.

Phenomenon of bacteriophagy: lysis and mutation of bacteria.

The phenomenon of bacterial lysis has been extensively studied in the case of cholera and plague. The stool of a patient recovering from cholera contains phage, and if a trace of such filtrated stool is introduced into a fairly turbid culture of cholera vibrios, this culture becomes perfectly clear after some time, all the vibrios being dissolved. Under the microscope this destruction of vibrios can be watched. It consists of swelling and spherulation of the organism, production of granules and finally disintegration of the bacteria. The clear liquid can again be inoculated into a fresh culture to obtain the same effect and the process can be repeated indefinitely. This illustrates the important characters of lysis of bacteria by bacteriophage, *i.e.*, its filterability, transmissibility and that it can be subcultured in series with living and growing bacteria.

The phenomenon of bacteriophage can be observed in young bouillon cultures of the cholera vibrio as well as in other media. In a solid medium and under suitable conditions there can be seen upon the surface growth of a certain number of more or less circular areas generally called plaques, within which no growth has taken place. These are the colonies of bacteriophage. They vary in size from that of a pin head up to 4 to 5 mm.; small-sized phages give rise to large plaques and large-sized phages to small plaques.

If the plates with their areas of plaques are further incubated, it is found that, after a certain time, small colonies develop in these areas. A similar phenomenon in the form of return of turbidity is observed in bouillon cultures rendered clear by phage. The explanation is that after a certain time secondary colonies of bacterial cultures develop which consist of strains of bacteria resistant to the action of phage.

The adaptation of bacteriophage to produce intense lytic action on bacteria is important. It is more commonly adapted to one particular species of organism though its affinity for more than one species has been observed. Therapeutically active phage should, therefore, be highly lytic towards the specific organism. This adaptation of phage towards the specific organism can be brought about by growing it with specific bacterial species till the lytic power is developed. If, however, the phage is originally weak the lytic power can be augmented by repeated passage with a substrate organism. This lytic power of phage is not unlimited, and the importance of the adaptation of bacteriophage towards bacteria can be realised from the fact that on it depends to a great extent the success or failure of the struggle that is going on between bacteria and the defensive mechanism of the host.

Bacteriophage is one of the most powerful agents in bringing about changes in the morphology, cultural and serological reactions of bacteria. These reactions are known as mutation and dissociation of bacteria and consist in alteration of motility and morphology, capsule

formation, proteolytic power, agglutinability, virulence, formation of filter-passing forms, etc. The main results of such changes are development of resistance to lysis, greater viability, and increased susceptibility to phagocytosis. According to d'Herelle, these alterations are brought on by bacteriophage, and are evidence of a reaction on the part of bacteria towards a pathogenic organism, which in this case is bacteriophage itself.

The modification of bacteria in this way may be so complete that secondary cultures from the original strain may be morphologically quite different. D'Herelle described extremely resistant and stable forms of cocci obtained by repeated transfers of young secondary cultures of dysentery, typhoid, paratyphoid, coli and cholera organisms. Hoder (1925) stated that there is definite possibility of transition of *Bact. coli* to paratyphoid-like forms. Doorenbos (1932) claimed the El Tor vibrio as a phage-modified form of cholera vibrio.

The conversion of non-haemolytic organisms to haemolytic forms, of agglutinating to non-agglutinating species by the action of bacteriophage, has been described by many workers. In the case of cholera, Pasricha and his co-workers (1931) state that there is some bacteriophage as well as serological relationship between the true cholera vibrio and the cholera-like forms. Many of these latter forms are considered to be only mutation forms of the true cholera vibrio and play a great part in the incidence of cholera. Morrison (1931), on the other hand, concludes from his experiments that the alterations in the cholera vibrio are due probably to the occurrence of bacterial contamination.

Specificity and types of bacteriophage. Burnett (1933) stated that bacteriophages are independent micro-organisms and differ widely in site and activity. d'Herelle considers that there is only one species of phage but that it is capable of a high degree of adaptation to pathogenic organisms. There may be races of phage with a specific affinity for a certain strain or a species of bacteria to the exclusion of all other strains of the same species, which procedure has been regarded as a valuable aid to the diagnosis of bacterial species.

Several types of bacteriophage have been recognised especially with regard to cholera. This is dependent upon the fact that with the development of a resistant series of bacteria on culture, a bacteriophage may be discovered which lyses these resistant strains. In this way, so far as cholera is concerned, several types of cholera phage have been recognised. In India, Asheshov called his types A, B and C; Pasricha and his co-workers (1932) have added types D, E and F to these already known ones.

Preparation of bacteriophage. The technique of bacteriophage study and the general principles of bacteriophagy are so highly specialised that they involve special methods and what first appears to be a highly complicated technique. In reality it is perhaps one of the simplest

techniques in the whole subject of bacteriology. It must be remembered that we are dealing with an organism which is so small in size that it passes dense filters which hold back all microscopically visible forms of life. This extreme minuteness of the bacteriophage corpuscle is of very definite advantage because it makes it possible for the bacteriophage to be separated from all visible forms of life by the simple process of filtration. Bacteriophage also possesses an additional property which is of extreme value in its preparation and study. It can only grow and multiply at the expense of living susceptible bacteria. Its food is the living bacteria and so far it has not been possible to devise any method for its propagation except on living material and those of its host.

Technique of filtration. This varies according to the nature of the fluid required to be filtered. It is generally done in the following way. Sterilised funnels with filter paper are filled with kieselguhr suspension. This leaves a very thin coating of kieselguhr on the filter paper, which retains most of the bacteria, giving an almost crystal clear solution. This clear filtrate is now filtered through porcelain candles under vacuum of 15 inches.

Isolation of bacteriophage. In order to isolate bacteriophage from stools, about 5 c.cm. of the stool, if liquid, or a small portion if solid, is mixed in a small flask containing broth (papain broth or any other liquid medium). If it is thought that the bacteriophage present is minimal, a few c.cm. of young peptone water culture of the organism, against which bacteriophage is sought, are added. The addition of fresh culture is made with the object of giving the bacteriophage present the opportunity to develop and thus to be more readily found.

Isolation of bacteriophage from water is done by following the same procedure. Large amounts of water may be necessary, and often preliminary filtration is required before the addition of 'enriching organisms.'

Rôle of bacteriophage. The phenomenon of death, recovery and immunity from diseases has been explained on the basis of development or absence of bacteriophage. d'Herelle believes that such a phenomenon is not dependent upon immunity, as is generally understood, but on the occurrence of bacteriophage. In the case of cholera, cases which do not develop bacteriophage die; cases with feeble bacteriophage, which disappears, also die; cases with strong bacteriophage at the outset recover promptly; cases with weak bacteriophage, which increases in potency, recover with some delay and the ups and downs in the clinical progress of the case represent the behaviour of

the bacteriophage. Bacteriophage by infecting bacteria, causes destruction and death of bacteria and is the direct agency of recovery of disease in man. By an indirect process it brings about a state of acquired immunity. Bacteriophage, by causing a solution of the bacteria, presents the bacteria in a condition to serve as ideal antigens. The lysates contain the lysed bodies of bacteria and induce in the body the mobilisation of the defensive forces.

If, however, the bacteriophage is not powerful enough or conditions are not suitable for the total destruction of the invading bacteria, then one of the two things may occur:—

(1) The bacteria may overcome the infection by bacteriophage, and develop an immunity against that particular bacteriophage and persist as avirulent saprophytes; in this condition they are entirely non-pathogenic. The question now arises whether these bacteria under any circumstances again become virulent and pathogenic. There is no direct evidence to either admit of this possibility or to define the conditions necessary for such changes to occur. It appears to be highly probable, however, that such changes do occur in nature and it is only rational to conceive that such changes should be the rule rather than the exception.

(2) The bacteria may not be able to completely rid themselves of the infection by bacteriophage, and although they develop an immunity against that particular phage, they lead a life in harmony with bacteriophage. There is a symbiosis between the causative organism and the bacteriophage and this results in attenuation of the virulence of the bacterium; such bacteria cause chronic disease. Acute diseases are due to young healthy disease-free or bacteriophage-free bacteria; chronic diseased conditions are caused by the diseased unhealthy phage-infected bacteria, which, in spite of their disability, yet retain sufficient invasive power to maintain a chronic diseased condition.

Such is the line of reasoning which has been advanced, but from the very nature and number of variable factors present, the proof of such conditions actually occurring is not very

convincing. *Bact. typhosum* in its active pure stage causes typhoid fever provided certain conditions exist under which it can exert its full invasive power, but *Bact. typhosum* contaminated with bacteriophage—the organism of the ‘carrier state’—may only cause a chronic infection such as cholecystitis. *V. cholerae*, when pure and healthy, kills a high percentage of those infected, but when parasitised by bacteriophage, the mortality rate is low or may cause very mild symptoms. *Past. pestis* kills rats when free, but when diseased it causes only a chronic form of plague. The theory of bacteriophage can even embrace a complete and consistent theory of acquired immunity, but these ideas should not be stretched too far in our present stage of knowledge.

Bacteriophage in prophylaxis of disease. d’Herelle has shown a very definite relationship between the occurrence of bacteriophage in nature and the incidence of certain intestinal diseases, particularly cholera and dysentery. At the beginning of the cholera season very few samples of waters collected from the river Hooghly and from the tanks in Calcutta show the presence of cholera phage. During the height of the cholera season the incidence of bacteriophage in nature increases till about 40 to 50 per cent. of the samples of water show the presence of powerful cholera phages. At the end of an epidemic, the whole bacteriological picture changes; instead of the cholera vibrio possessing typical characters which may be likened to a well-organised army, there are towards the end of an epidemic, a heterogeneous group of organisms varying in their power, some difficult to recognise as vibrios, which are like the ragged disorganised members of a worn out army. All the factors that bring about this change are not known, but it is known that this enemy of man, the cholera vibrio, has been in conflict, amongst other forces, with bacteriophage which has played an important part in disorganising the invasion of the cholera vibrio. The course of a cholera epidemic is a struggle between vibrio and phage for dominance, and the ups and downs of an epidemic are the visible effects of that stupendous invisible battle that takes place in nature. The battle-ground is the intestine of man.

This concept of prophylaxis and immunity is so radically opposed to our ideas of epidemiology that at first it is difficult to appreciate its importance. It must be realised now that there exist in nature two very distinct forces—one, certain bacteria which are harmful to man and that the source of these harmful bacteria in the majority of instances is man himself; the other, another living force, which because it is harmful to bacteria is of distinct value to man. This second force is, as it were, provided by nature to maintain a state of equilibrium between man and his bacterial enemies. It is a police force provided by nature to guard mankind in times of stress. If conditions are favourable this force of bacteriophage multiplies so readily and becomes so powerful that it brings to an end the supremacy of the bacteria.

These theories raise very important points both in the prophylaxis and treatment of epidemic diseases. From this point of view the question arises whether the propagation of bacteriophage is advisable. To do this are we to allow the unhampered dissemination of natural bacteriophages which would necessitate the cessation of all public health activities, and to rely entirely on the results of the natural adjustment between the bacteria and the bacteriophage? These last factors may be so variable that it would not be justifiable to allow the cessation of the stringent sanitary measures. The bacteriophage as it exists in nature has had centuries of free play, unhampered by any sanitary measures, and we still have big epidemics of intestinal diseases. Secondly, the bacteriophages as they exist in nature may be supplemented by specially trained and highly virulent bacteriophages. In this way it may be possible to marshal together the natural enemies of bacteria, and harness nature for the benefit of mankind. This certainly must appeal to everyone as the most rational point of view. Experiments in the laboratory and trials with bacteriophage in the field, both as a prophylactic and therapeutic agent, have been undertaken by several workers, and although bacteriophage prophylaxis and therapy have made great progress, the subject is still under trial and no definite conclusions can be drawn from the experiments reported so far.

One thing can be definitely stated and that is that the results of the trials so far are not against bacteriophage; there is evidence highly suggestive that bacteriophage is of value. Though great hopes were raised at first of the therapeutic value of bacteriophage, the results so far have not fulfilled these hopes. Great things are still expected from bacteriophage which on purely theoretical grounds possesses all the attributes of an ideal internal antiseptic. It has no action whatsoever on any living tissue, kills the invading organism rapidly and increases in amount as it does so. The conditions within the body may and do modify the effectiveness of its attack, but it is hard to believe that an active phage can be entirely without effect on the course of an infection by a sensitive organism.

Therapeutic uses. As early as 1921 bacillary dysentery was treated with administration of bacteriophage and since that time various results were obtained with this form of therapy.

According to d'Herelle, in the bacteriophage there is a natural therapeutic agent which is of value in the cure of disease as well as in prophylaxis. It has already been pointed out that an active specific phage possesses all the attributes of an antiseptic, and it kills the specific organism against which it is employed and increases in amount during this process. From this point of view it was considered a valuable therapeutic agent in bacillary dysentery, cholera and various other bacterial diseases. Unfortunately the success with bacteriophage treatment is not uniform and its usefulness has been disputed by many workers. It is said that the action of bacteriophage is brought about by purely chemical means and that the effects produced are nothing but a reaction due to the introduction of a foreign protein. Topley, Wilson and Lewis (1925) used bacteriophage in strictly controlled experiments with mouse typhoid infection. Their observations were that the presence of bacteriophage does not prevent the spread of infection, check an epidemic when it has once started, or appreciably reduce the mortality. They further found that there is no evidence of development of immediate immunity either from infection or ingestion of bacteriophage.

The majority of those who are however willing to accept d'Herelle's hypothesis are of opinion that bacteriophage is a living ultramicroscopic virus which is capable of being a parasite on bacteria and which is said to dissolve and destroy them through the agency of a ferment it secretes. In addition to its direct action on bacteria, bacteriophage may also exert an indirect action by increasing the phagocytic power of the leucocytes, the explanation being that the lysins secreted by bacteriophage are really of the nature of opsonins. The cultures of bacteria lysed by bacteriophage have been considered to act as highly effective vaccines because of their capacity to produce antibodies possessing a far more protective power than the antibodies obtained from ordinary bacterial vaccine. The bacterial split products obtained under the action of bacteriophage are in a physical or chemical state highly suitable to induce a strong and durable immunity so that this immunity adds indirectly to the value of bacteriophage as a therapeutic agent.

According to d'Herelle many of the unsuccessful results of bacteriophage therapy are due to the inadequate technique in the preparation of phage. Only the virulent type of bacteriophage is effective and hence it is either therapeutically effective or without effect.

The rôle of bacteriophage as a therapeutic agent is as yet complex. Satisfactory results can only be obtained by following certain procedures. It is to be understood that there is an essential difference in principle between the treatment of acute and chronic infectious diseases with bacteriophage. In cases of acute disease a powerful bacteriophage must be brought into contact with the pathogenic bacteria before they have had opportunity to produce sufficient lesions to cause death. Chronic cases possess a different aspect altogether from the point of view of bacteriophage treatment. In this condition a state of partial symbiosis exists between the infecting bacteria and the phage and in order to bring about a full therapeutic effect a race of bacteriophage has to be employed which is virulent for the bacteria.

The mode of administration and dosage of bacteriophage requires some consideration. Bacteriophage, to be of any value, should be administered as early in the course of the disease as possible. Bacteriophage must come into direct contact with the invading organism and hence in intestinal disorders it should be given by the mouth. In cases of infection of the urogenital tract bacteriophage has to be introduced directly into the bladder, localised infections of subcutaneous or deep tissues require the direct application of bacteriophage in the infected focus. With regard to dosage and frequency of treatment it may be stated that the amount of bacteriophage to be given depends upon the virulence of the bacteriophage employed. This is due to the fact that bacteriophage in the presence of susceptible organisms perpetuates itself and the amount administered does not determine the amount that will ultimately develop. In case of acute infections a few administrations may be sufficient while in chronic types of infection bacteriophage therapy may have to be continued over a long period.

Bacillary dysentery. The treatment of bacillary dysentery with bacteriophage is now widely recognised. Fletcher tried bacteriophage in 22 cases of Flexner infection, but the treatment was a failure, while in the Shiga type of infection the bacilli disappeared from the stool on the second day of the disease. Morison, however, obtained encouraging results in an epidemic of dysentery; 70 cases were treated with 2 c.cm. of bacteriophage three times daily and of these three died and the rest were all cured. The author has treated a large number of cases of both acute and chronic dysentery with bacteriophage with indefinite results. In a few cases the effect produced appeared to be marvellous, but in the majority of cases no improvement could be detected. The results of trials by various observers, however, appear to indicate that bacteriophage therapy in bacillary dysentery is worthy of further trial.

Cholera. Bacteriophage therapy in cholera has been advocated. In this connection it is worthy of note that the therapeutic phage employed in the treatment of cholera must be virulent. The existence of a case with virulent bacteriophage should therefore draw special attention. Along with this must be considered the vibrios; some may yield to a phage of higher virulence while others may lead to actual diminution in the virulence of the bacteriophage. In order to obviate this difficulty Asheshov recommends a method of keeping therapeutic phage virulent by repeated cultivation on a freshly isolated vibrio.

The results published by d'Herelle and others (1930) who investigated the problem of bacteriophage treatment on behalf of the Government of India, appear to be striking enough. In a total of 198 cases, 74 received bacteriophage treatment, of whom only 6 died; while in a series of 124 cases not receiving the phage treatment the mortality rate was 78 per cent. Morison and Vardon (1929) used a combined dysentery-cholera bacteriophage in two epidemics of cholera in Assam. A mortality of 75.8 per cent. resulted in cases having no bacteriophage, while the death rate was 29.0 per cent. in cases receiving bacteriophage treatment. They mostly employed 2 c.cm. of phage four times daily by the mouth and serious cases received 2 c.cm. along with hypertonic saline. Souchard (1930) on the other hand failed to obtain any benefit and in his series a mortality of 24 out of 27 resulted.

The therapeutic efficacy of bacteriophage in epidemic cholera as investigated by Morison (1932) is worthy of note. Two areas were selected, keeping one as control. In the test area receiving bacteriophage, the district remained free from cholera for five successive epidemic seasons, while in the control area there was one outbreak each season. The account given by Asheshov, Khan and Lahiri (1931) gives a very promising picture of the bacteriophage treatment of cholera, coupled with simultaneous administration of hypertonic saline. Their method of treatment lies in giving bacteriophage in one drachm doses every 30 minutes, the bacteriophage being given undiluted and sipped directly from the bottle. Two bottles of bacteriophage, each containing 50 c.cm., should be finished in 16 hours, during the following 24 to 48 hours another bottle may be taken. They also employed bacteriophage by the intravenous route, in doses of 5 c.cm. considerably diluted, in order to prevent the occurrence of anaphylactic shock.

Although there is some evidence to show that bacteriophage may be of definite therapeutic value, further systematic work is necessary before any definite opinion can be given regarding its efficacy in the treatment of cholera in epidemic form.

Enteric fever. Contrary to the favourable results obtained with bacteriophage therapy in the infections of the intestinal canal such as dysentery and cholera, its efficacy in enteric fever is doubtful. Some clinicians have reported excellent results. Strains of phage virulent to the organism *in vitro* under laboratory conditions have been obtained, but these may be entirely ineffective in actual treatment of the disease. There are, however, occasional favourable reports with bacteriophage treatment. The usual dosage in such cases is 2 c.cm. of the phage three times daily for four to five days. Intravenous injections of the phage have been resorted to, to lower the temperature and hasten recovery. In view of these results and of the diverse reports that have been published regarding bacteriophage therapy in typhoid and paratyphoid

fevers, the question of application of bacteriophage in the treatment still remains unsettled.

Plague. The treatment of plague by bacteriophage has not as yet been carried out on a large scale and its value is therefore still undetermined. d'Herelle reported successful treatment of four cases of bubonic plague and stated that this method of treatment offers much promise. Couvy and his co-workers (1930 and 1932) reported favourable results of treatment in severe cases of human plague with a polyvalent phage. They affirmed the perfect safety of treatment of plague with bacteriophage even by intravenous injection. Two hours after injection of the phage, *Past. pestis* are found to be in a state of lysis. Pons (1932) reports very interesting results with bacteriophage therapy. He states that bacteriophage when given subcutaneously is rapidly generalised and produces lysis of the plague bacilli in 24 hours. As long as the lytic principles are present, blood or the aspirated material from the bubo remains sterile. Other workers have failed to substantiate these claims. Compton (1928) tried bacteriophage in experimental plague of animals but obtained indifferent results. Pirie (1929) stated that there is little evidence in support of either therapeutic or prophylactic value of bacteriophage in plague. Naidu and Avari (1932) had little success with a strain of powerful bacteriophage in human or in animal plague. According to d'Herelle, however, the bacteriophage therapy may constitute the specific treatment for plague; 1 to 2 c.cm. of virulent bacteriophage culture should be injected as soon as possible. The differences in results, according to him, may be attributed to the fact that in many cases the bacteriophages employed were several weeks old, and were not, therefore, sufficiently potent to deal with specific types of *Past. pestis* which may be extraordinarily virulent. As it is not possible to identify the organismal type before use of a phage in plague, all workers now emphasize the necessity of using a polyvalent potent phage. Very encouraging results, with comparatively little reaction, have been obtained in plague with a polyvalent bacteriophage. In bubonic plague the bacteriophage is administered subcutaneously and into the bubo in doses of 2 to 3 c.cm. on the first day and again on the second day; on the third day it is given subcutaneously. In septicæmic plague 3 c.cm. of phage have been given in the course of 24 hours, repeated if necessary within three days. Recent experiments (unpublished) on mice carried out in the Haffkine's Institute have shown that bacteriophage has no protective or curative effect in infection with *Past. pestis*.

Pyogenic Infections. Certain favourable results are also reported in localised septic conditions due to staphylococci and streptococci. Furunculosis, carbuncles, abscesses, osteomyelitis and miscellaneous infections have been treated by this method. The usual procedure of application of bacteriophage in these cases is to administer it by subcutaneous injection, although a few investigators have combined such injections

with the local application of bacteriophage in the form of moist dressings. Usually two injections, each of which may vary from 0.5 c.cm. to 3 c.cm., have been given with an interval of from 24 to 48 hours. In the case of *Bact. coli* infection of the bladder, this method is said to have given very encouraging results. Larkum (1926) demonstrated the existence of bacteriophage in most acute urinary infections and he later tried this method of treatment in suppurative conditions and found it satisfactory.

Certain general principles must be borne in mind for the clinical use of bacteriophage in these conditions. It must come into direct contact with the infected tissues and external application, direct injection and circum-injection are employed according to the type of lesions to be dealt with. Care should be taken during injection of bacteriophage inside a closed cavity, so that the tension is not thereby increased. It is, therefore, always safer to aspirate such pus as may be present in it, before injecting the phage.

Though bacteriophage treatment by localised injections has given a certain measure of success, it is not at present possible to evaluate its importance in clinical practice. In these conditions there is direct contact between the invading organism and the therapeutic agent in the shape of bacteriophage, and it is not possible to say how far the results are due to bacteriophage therapy or other bacterial products that are present.

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CHAPTER III

BOWEL DISEASES

The varying conditions of oxygen tension and reactions, physical and chemical, in different levels of the alimentary canal favour the growth of different types of organisms at these various levels of the intestines. The mouth offers an aerobic area, although the various crevices between the teeth, in the folds of the mucous membranes and the crypts of the tonsils, anærobic organisms flourish. In the stomach, if the acidity of the gastric juice is normal, most bacteria are killed unless otherwise protected. In the duodenum oxygen tension is low and from here onward to the colon, more or less anærobic conditions prevail. In the colon and rectum conditions are favourable for the growth of aerobic organisms. Certain conditions influence the normal bacterial flora of the intestine, *e.g.*, the degree of digestion of the food, the proportion of unaltered carbohydrates and protein at different levels of the gut, etc. The products of bacterial growth at one level of the colon will also influence the growth of other types of organisms in the same level and further down. Although a new invader may sometime succeed in establishing a foot-hold at some level in the gut, it has to encounter other bacteria at lower levels, and unless conditions are particularly favourable, it will be readily overpowered by the more adapted intestinal bacteria. In the colon and rectum many of the bacteria die out as a result of the gradual loss of water. The presence of bacteriophage also helps to maintain an equilibrium between man and his intestinal bacteria.

At birth there are no bacteria in the intestine, the meconium is sterile unless infection has taken place as a result of some general infection in the mother. Shortly after birth bacteria make their appearance. They are chance contaminations, from kissing, feeding bottles, milk, etc., and are of various kinds (staphylococcus, streptococcus, coliform organisms, yeasts, etc.). In a few days after birth the characteristic intestinal flora is

established which is modified under different conditions, such as administration of cathartics, changes in diet, intestinal infections. The principal types of intestinal flora are, *B. bifidus*, *Lactobacillus acidophilus*, *Streptococcus faecalis*, certain spore-bearing aerobes and anærobies, coliform and other allied organisms. The intestinal flora varies with the conditions of life. In breast-fed infants the duodenum contains streptococcus, while in the rest of the gut coliform organisms and *B. bifidus* are common. In the artificially-fed infants Gram-negative organisms are numerous and putrefactive bacteria are relatively more common. The duodenum of a normal person is relatively sterile except during digestion. In the upper part of the small intestine cocci predominate and the lower part contains an abundance of coliform organisms and spore-bearing proteolytic aerobes. The large intestine contains certain proteolytic anærobies and aerobes, yeasts, moulds and spirilli.

The intestinal flora is, however, subject to wide variations. In infections with cholera and dysentery the specific infecting organisms may dominate the intestinal flora. Changes in diet, such as increase of carbohydrates may lead to a preponderance of intestinal flora of *Lactobacillus acidophilus* type. Meat protein leads to an increase of the putrefactive bacteria; milk and vegetable proteins produce much less putrefaction. Purgatives and the so-called intestinal antiseptic group, have no appreciable effect on the intestinal flora. Though direct entrance of the bacteria to the gastro-intestinal canal is no doubt the most important route by which infection occurs, it has been argued that infection may occur also through other channels. If bacteria are injected parenterally they can be found in the bile, and if the bile duct is tied, certain bacteria are eliminated through the intestinal mucosa.

Foster and his co-workers (1908) in their study of the mode of infection of the intestinal canal with typhoid bacilli put forward the view that the bacilli enter the circulation possibly through the tonsils. They multiply in the blood, pass through the liver and gain access to the gall bladder where they set up a catarrhal inflammation, and thence infect the intestine. They showed that when typhoid bacilli were injected intravenously

into animals the organisms were found mainly in the gall bladder where they persisted for weeks. *Bact. typhosum* could be isolated from the blood in the later parts of the incubation period before any manifestations of disease appeared and before they could be isolated from the intestine. On autopsy, the bacilli were always present in the gall bladder and the upper parts of the intestine, but were frequently absent in the lower part of the intestine.

Recently, Teal (1934) has investigated the problem of bacterial infection of the intestinal canal. He administered the bacteria to animals by different channels and noted the results. It was found that bacteria can find their way to the tissues through the bucco-pharyngeal mucous membrane without any breach occurring on the surface. They multiply in the neighbouring lymphatic glands, enter the blood stream and from there reach the intestinal mucosa and are excreted along its entire length. Most of the organisms when given by the mouth are destroyed by the gastric juice because the intestinal bacilli are incapable of long survival in an acid medium. When the pH is considerably lower than 3 or 4, death of bacteria occurs rapidly. A small number may however pass alive through the pylorus and reach the intestine. When the organisms are injected directly into the intestine at places where the acidity is neutralised, the bacteria may survive for a considerable time, but the normal healthy mucosa as a rule does not allow their passage readily and those that pass through are rapidly destroyed in the lymphatic glands. Loudon and Sanarelli showed that germicidal activity in these cases is not due to the acidity of the gastric juice but to other factors, *e.g.*, the sterilizing effect of the succus entericus; the presence of normal non-pathogenic organisms in the gut, however, plays an important part in inhibiting the growth of pathogenic bacteria.

Another important consideration in this connection is the impermeability of the healthy mucosa to intestinal organisms. This property probably comes into play in nearly all cases. If, however, the mucous membrane is injured, the passage of organisms through it is facilitated. Besredka was able to

demonstrate the passage of bacteria through the mucous membrane of the intestine after damaging it with large quantities of ox bile. It thus appears that sufficient protection exists in nature for the prevention of intestinal infections. In cases of typhoid fever infection is caused by the bacteria escaping the action of hydrochloric acid in the stomach. This occurs when they are hurried through the stomach in a large quantity of water, or in the presence of some organic envelope, or by hypochlorhydria, temporary or permanent. In the intestine some alteration in the permeability or resistance of the mucosa brought on by such factors as injudicious diet, contaminated food and conditions reflexly altering the circulation of the mucosa, also favour the development of an infection. In addition, it has been suggested that in some cases infection takes place by passage of the bacilli through the bucco-pharyngeal mucosa followed by invasion of the blood stream. In bacillary dysentery, infection occurs through the oral route. The toxins of *Bact. shigæ* are not destroyed in the gastro-intestinal tract. The exotoxin is absorbed into the blood stream and can cause typical damage to the capillary endothelium, the central nervous system and the endocrine glands; the endotoxin which causes intestinal lesions is eliminated by the large intestine. The living bacilli can produce toxins sufficient to cause damage to the mucous membrane, and allow multiplication of the organisms. In the case of cholera, ingestion of the bacilli is necessary for the production of the disease. Although this is true, there seem to be certain conditions which modify an infection. The state of health of an individual and the degree of acidity of the stomach contents determine, to a great extent, the susceptibility or otherwise to an infection.

General management. The rationale of the treatment of bacterial infection of the intestine, properly considered, is the management of the patient rather than of the disease. Every attempt should be made to increase the patient's resistance. Constipation is to be particularly avoided. Anything which lowers the neuro-muscular tone of the intestinal wall will contribute to the development of constipation. Seasonal changes, lack of essential food factors, want of exercise, excess of tobacco,

lack of efficient mastication and deficiency in the intake of fluid are important contributory factors. Undoubtedly the nature of the dietary is of utmost importance. So far as the food factor is concerned, an adequate supply of fresh foodstuffs including an ample supply of vegetables and fruits is essential. The nature of the diet is dependent upon the specific illness, but in general, it may be said that rough fibrous meat and fish and the coarser and harsher vegetables and fruits should be forbidden. The softer forms of meat and fish and the simpler fruits and vegetables are permissible. Sugars and sugar-producing foods, by reason of their fermentable qualities should be reduced. The main articles of consumption should be restricted to milk (citrat-ed if necessary), raw or lightly boiled eggs, butter and cheese in moderate quantity which provide both protein and fat. The important point in the management of a case should be to soothe and not to stimulate the intestine, and such an effect can only be attained by presenting the intestine with a small and innocuous mass of food which it can easily digest.

In cases where the intestine is sluggish some laxative may be prescribed to empty the bowel. The choice of laxatives in cases of stasis is not always easy, because most of these drugs have no effect. Liquid paraffin is suitable in some cases; it should not, however, be used indiscriminately or persisted with too long, because besides being useful as a lubricant it can do harm by retarding absorption. Some general metabolic stimulants do good in asthenic cases; thyroid extract may be prescribed as a general stimulant. Autogenous vaccine prepared from any pathogenic organisms isolated from the fæces may be employed in conjunction with other remedies.

Intestinal antiseptics in bacterial infection. It is now generally admitted that intestinal antiseptics are of no value and there is no drug known which, when administered by the mouth, will reduce the number of living bacteria in the stools. Nevertheless, it is possible that some drugs may check or diminish the growth of bacteria in the upper part of the intestine and thereby lessen the absorption of toxic products. With this idea disinfection of the alimentary canal has been advocated in many diseases such as cholera, typhoid, dysentery, etc.

Normally the lower one-third of the small intestine and the upper part of the large intestine contain the largest number of bacteria, and the number of living bacteria steadily diminishes further down in the colon. Many experiments have been conducted to determine the bactericidal effect of various drugs on the intestinal flora. Rogers (1913) tested the efficacy of certain inorganic and organic compounds of silver, copper and mercury and some other antiseptics on Shiga's bacillus and concluded that silver compounds such as albeigin, gave the best results, mercury and copper compounds being non-effective. Of the other antiseptics, cyllin and izal are effective both in broth and in distilled water and are worthy of further trial. Phenol and the higher coal-tar products have also an antiseptic property, but most of them lose their activity in the presence of faeces and thus fail to exert any influence on the intestinal bacteria. This can be readily understood if we consider the large number of bacteria present in the colon and the large mass of material in the intestine which tend to weaken the antiseptic property of the drugs. Besides many of the so-called intestinal antiseptics produce toxic symptoms in doses necessary to produce any bactericidal effect.

There is another important point to be considered in this connection. The normal defensive power of the healthy mucosa is always brought into action to deal with the bacteria present in the gut. These drugs therefore may on the contrary do harm by injuring the intestinal mucosa. This has been demonstrated by Schutz (1901) who found that after large doses of calomel the cholera vibrio persists in the intestinal canal of dogs for a longer period than when no drug is given.

Although complete intestinal asepsis is not practicable, a relative asepsis is not inconceivable though it has not been demonstrated satisfactorily. The use of antiseptics, at best, is inferior to other methods, such as suitable modifications of diet and evacuation of the bowel. Whenever any drug is used those antiseptics should be preferred which are sparingly soluble in water so that they will not be absorbed from the intestine to any appreciable extent. In order that a drug may be useful as an intestinal antiseptic it must exert

the maximum effect on the colon where the action is desired without its action being hampered in the presence of organic matter. It must at the same time be non-irritant to the gastric and intestinal mucosa and should not be absorbed to an extent sufficient to produce toxic symptoms. The following are some of the drugs commonly used:—

Potassium permanganate. It is an oxidising agent and disinfectant but its action is weakened by the presence of organic matter. As a disinfectant to the intestinal canal it was used by Rogers in cholera. In order to destroy the toxins in cholera the doses recommended are as much as 50 gr. a day. This is given in the form of pills made up with vaseline in doses of 2 gr. every fifteen minutes for two hours, then every half-hour till the stools are coloured green. Large doses of the drug produce toxic symptoms and hence it should always be used with caution.

Kaolin. This compound is the native white aluminium silicate purified by elutriation from sandy matter; another variety of it is known as Fuller's earth. Kaolin and Fuller's earth are adsorbents and as such have the power of absorbing various soluble substances and suspended matters. The drug has been largely used in diarrhoea, dysentery and cholera. It is not a direct disinfectant of the alimentary canal but is believed to adsorb bacterial toxins and affords a mechanical protection for the inflamed mucous membrane.

Salicylic compounds. Of these salol (phenyl salicylate) is largely used as an intestinal antiseptic. It is non-irritant to the stomach and is broken up liberating phenol and salicylic acid. The phenol component is thought to be valuable from the point of view of its effect on the disinfection of the gut, but the decomposition is so slow and the absorption of phenol is so rapid that its usefulness is very limited. When given by the mouth nearly 10 per cent. or more is excreted unchanged in the faeces; when administered in a capsule it may be found in the faeces as crystals, formed by partial fusion and recrystallisation of the drug. It is therefore advisable to give it in the form of an emulsion or with some indifferent powder. The dose is 5 to 20 gr. by the mouth. It has been largely prescribed in typhoid fever, but it is doubtful whether it has any effect on the disease.

Phenol and its derivatives. The substances of this group are highly bactericidal. The higher coal tar products have great germicidal power and they have a much feebler toxic action when given by the mouth as compared with phenol. Some of these compounds such as tetrachlor-phenol, o-cresol, tetra-brom-o-cresol have very high phenol co-efficients, but they lose their disinfectant property in the presence of organic matter and hence are not used therapeutically.

A few benzol derivatives have been used internally. Naphthalene and the less-irritating related compounds are among the most effective. Alpha-naphthol is highly toxic and is not employed; beta-naphthol acts similarly to phenol but is more germicidal. It is given in doses of 3 to 10 gr. and as much as 10 to 15 gr. may be given in a single dose, but it is liable to set up gastric disturbances and upset digestion. Other preparations such as benzo-naphthol and naphthol-bismuth have also been used.

Miscellaneous drugs. Insoluble salts and slightly soluble salts of the heavy metals are also available as indirect intestinal antiseptics. Large doses of bismuth are used in diarrhoea and intestinal disorders. The action of bismuth is partly mechanical by virtue of its power of forming a protective covering on the inflamed mucous membrane and many insoluble salts will do it. A small amount may however be dissolved and exert an astringent and mild antiseptic action. Bismuth carbonate and subnitrate are generally used and may be prescribed either in the form of a powder or suspended with mucilage.

Insoluble salts of mercury especially those which have a cathartic action have also some antiseptic property. Calomel is a cholagogue purgative and is therefore useful in conditions of intestinal putrefaction, *e.g.*, in dysentery, early cases of typhoid. Asiatic cholera has been treated in the early stage with divided doses of calomel. Bile is another substance which has been used as an antiseptic. It is not a direct disinfectant of the gut contents but an indirect one by aiding digestion, and helping absorption of foodstuff. In cases of biliary obstruction with offensive stools, bile is said to be useful. Ox-bile is a dark greenish brown substance somewhat bitter in taste. It is prescribed in doses of 5 to 15 gr.; the antiseptic value is however doubtful.

Charcoal has been used as an intestinal antiseptic. It has the power of adsorbing gases and this has led to its use for flatulence and indigestion. In acute bacterial dysentery, large doses are given, 30 to 45 gm., three times daily, mixed with hot tea. *Carbo animalis* or bone black is preferred for this large dose, because the sharp particles of the vegetable charcoal act as an irritant. It has been experimentally shown that both diphtheria toxin and antitoxin are absorbed by animal charcoal. In general the toxins of the Gram-positive bacteria are said to be more readily absorbed than those of Gram-negative ones. It may therefore be advantageously prescribed in those cases associated with much bacterial fermentation in the intestinal canal.

ENTERIC FEVER

Enteric fever constitutes a group of continued fevers caused by *Bact. typhosum* and a group of closely related organisms amongst which the most important are *Bact. paratyphosum*. A

and *B. Bact. typhosum* is the causative organism of typhoid fever and the other organisms of paratyphoid fevers; the term enteric fever is commonly employed to include the continued fevers due to these organisms.

The generic name enteric fever is also a convenient name as it is often impossible to distinguish these fevers clinically. Generally infections due to the paratyphoid group of organisms are milder and less fatal than typhoid fever; but recent work has shown that some of the fevers due to the so-called paratyphoid group of organisms are of more serious import than the classical typhoid fever. During recent years considerable data has accumulated concerning the distribution of various types of enteric infection and without entering into the details of the distribution of the different types it may be said that these fevers have a world-wide distribution. The more the attention of workers is directed to the study of these fevers the more it is being realized that a number of organisms, more or less related to one another, are implicated in the causation of these fevers and that they have a much larger area of distribution than was formerly believed.

The enteric group of fevers occur throughout the year in the tropics and during the hot and moist periods of the year they tend to occur in epidemic form. Wherever sanitation is deficient and there is neglect of the proper disposal of fæces, and wherever there is a lack of safeguarding of the water supply, there is a danger of an outbreak. The bacilli may reach the mouth by means of infected fingers or by the intake of infected food and water. Outbreaks have been traced to the eating of raw contaminated oysters, to food contaminated by flies and to the use of contaminated ice.

In every case, however, the infection is from the urine or fæces of a typhoid case, or to carriers who play an important part in the spread of the disease as will be realised when it is remembered that some 2 to 5 per cent. of those who contract the disease become more or less permanent carriers and continue to excrete the organisms for many years.

Typhoid fever, due to *Bact. typhosum*, may be taken as a representative of the group of enteric fevers as a whole. The

paratyphoid infections are milder and will not be considered separately. The basis of therapy is the same in all the enteric fevers.

Bact. typhosum the causative organism of typhoid fever is a motile flagellated bacillus and produces an intracellular toxin. It gives a specific agglutination reaction which is of great value in the diagnosis of a case of typhoid fever. The bacillus does not withstand high temperature, being killed at a temperature of 60°C. It is however resistant to cold and can live for about three months in ice, but in ordinary tap water it usually disappears within two to three days. The duration of life of the bacteria is of great practical importance, though it must be remembered that it varies with the amount of movement of water, the chemical substances present and various other factors, such as the existence of saprophytic organisms. The bacilli have been obtained from the soil. In faeces their duration of life is variable, being dependent on the chemical character of the stool and other bacilli present. In man the infection occurs through swallowing contaminated material. The bacteria pass the acid barrier in the stomach, multiply in the upper part of the small intestine in bile, pass through the lymph follicles with resulting hyperplasia, and in severe cases, ulceration, sloughing and necrosis may occur. The bacilli then gain entrance *via* the lacteals to the posterior abdominal lymph glands any lymph glands of the mesentery which become enlarged. Later, they invade the blood stream with transitory or intermittent primary bacteraemia, and formation of foci in the spleen, liver and bone marrow where they grow. From these foci the bacteria invade the blood again, causing secondary bacteraemia and this occurs in the first week of the disease and later a secondary invasion of the intestines occurs. The bacilli are excreted from the blood into the bile and in the urine in nearly all cases. The duration of the organisms in the blood varies, they can be occasionally cultivated after the first week of illness. In many other sites their occurrence has been observed, e.g., in the rose spots, in the abscesses in the skin, subcutaneous tissues and suppuration in various parts of the body. Their occurrence in the urine is important and it has been observed that in about 25 per cent. of cases the bacilli may be found in the urine but not until the third week and in some patients not until convalescence. The stage of recovery coincides with the period when the patient shows antibodies in the blood. Gradually the various foci of infection, gall bladder, spleen and kidney clear up, but in some cases if a focus is left behind the carrier condition develops and the patient becomes a source of infection to others.

The paratyphoid bacilli are closely related to *Bact. typhosum*. There are several varieties of which A and B are the common types. Though the clinical features of paratyphoid fever are much the same as those of typhoid fever, the essential difference lies in the course

being varied and irregular and the infection, as a rule, is milder with a low mortality. In paratyphoid fevers the intestines frequently show no change, although in some cases they may be acutely inflamed throughout their length.

Carrier. The rôle of the 'carrier' in the spread of infection is important. Some 2 to 5 per cent. of those who have recovered from an attack of enteric fever, continue to pass the specific organism in the excreta sometimes for years. In some individuals the bacilli may be found in the excreta without the patient having, at any period of his life, suffered from the disease. The carriers are a grave danger to the community. They contaminate the food or water supply and spread infection. The main conclusion which emerges from the mass of evidence on record is that the ultimate source of infection would appear in all cases, to be the excreta of an infected human being and this source is seldom remote. These observations and similar ones in different parts of the world go to prove the importance of isolating typhoid convalescents until they are found to be no longer excreting typhoid bacilli in the stools. It is a difficult matter to treat these carriers. The intestinal antiseptics, such as hexamine, usually fail to cure them and similarly vaccine treatment is also uncertain. The removal of the gall bladder has been advocated but this is a serious procedure and very few will submit to such a major surgical-interference.

Laboratory diagnosis. The actual isolation and identification of the infecting organism is the best direct evidence of typhoid fever. All immunological methods, such as agglutination test, are strongly corroborative, but should be considered as subsidiary to the isolation of the organism by blood, stool and urine culture. Within the first few days of fever (chances are less after the 5th or 6th day) culture of the blood generally gives positive results. The blood is cultured in ox bile at 37°C. (5 c.cm. blood to 25 c.cm. bile) sub-cultured on solid media and the organism identified by biochemical and agglutination tests; culture can also be done in 10 per cent. glucose broth (10 gm. to 100 c.cm. broth). The stool may give positive results within 3 or 4 days of the onset of the disease but more frequently after the second week. A fresh stool should be examined or it may be preserved in Teague and Churmna's solutions; malachite green, china green, etc., if added to the stool inhibit the growth of other coliform organisms. The stool is emulsified in peptone water and then plated on MacConkey's medium. Isolation of the organisms from urine is possible during the second and third week and is done in the same way as for stools. The agglutination reactions (better known as Widal's test) may be performed by the macroscopic or the microscopic method, but the former is preferable. The principle of the reaction is to mix increasing dilutions of the serum with the bacterial emulsion and examine for agglutination. The agglutinins usually appear during the first week and attain their highest titre from the 10th to 14th

day and then gradually fall. It is necessary to determine the 'O' as well as the 'H' agglutinins. Some typhoid patients develop somatic but not flagellar agglutinins and this may be missed if both are not looked for. 'O' agglutinins may appear early but negative results in the first week are of little importance. It may be noted in this connection that inoculated cases show much higher titre for H than O whereas in un-inoculated cases positive results with 'O' at 1 in 20 to 1 in 50 are more common than with H. To do a complete test according to the present state of our knowledge nine suspensions should be used and these are :

- (1) Formolised broth suspension of *Bact. typhosum*.
- (2) " " " *Bact. paratyphosum A*
- (3) " " " type phase of *Bact. paratyphosum B*
- (4) " " " " *Bact. paratyphosum C*
- (5) " " " " *suipestifer*.

The above are H suspensions

- (6) Alcoholised suspension of *Bact. typhosum*.
- (7) " " " *Bact. paratyphosum A*
- (8) " " " *Bact. paratyphosum B*
- (9) " " " *Bact. paratyphosum C*

These are O suspensions

The ideal test for the enteric group of fevers should include all these, but for routine purposes, the first three, or better still, the first six may be used, repeating the test with the others later, if necessary. Only smooth cultures must be used for preparing the emulsions. The occurrence of a positive Widal reaction after the first week of illness and its maximum about the twenty-first day, is diagnostic. Interpretation of the results is as follows. In the un-inoculated cases of typhoid fever a positive reaction up to a titre of 1 in 100 is highly suggestive, and 1 in 500 is almost a certain indication ; positive reaction may be obtained up to a titre of 1 in 50,000. In case of infection with *paratyphosum B* the results are similar, but agglutination may occur up to a titre of 1 in 500,000. For *paratyphosum A*, positive reaction in 1 in 20 is significant and in 1 in 100 almost certain. It is rare in higher dilutions. In the inoculated cases serial tests should be done ; a four-fold rise in titre in the early stage is not of much value but a ten-fold rise is strongly suggestive. A positive reaction in an 'O' titre of 1 in 100 or higher is of important diagnostic significance and in 'H' titre of 1 in 1000 to 1 in 2000 is also suggestive.

Diarrhoea reaction. The reaction is present from the fourth to the fourteenth day in typhoid. A negative reaction is of more value against the diagnosis than a positive reaction is in favour of it. It is of more import in distinguishing between a relapse and a complication. The

reaction is present in measles but not usually in German measles. It is very constantly present in tuberculosis which is advancing very rapidly. The test is done in the following way. Equal parts of the diazo-reagent and urine are placed in a test tube and covered with a little ammonia. If the liquid becomes deep red in colour at the junction of the two fluids and upon shaking a pink colour be imparted to the foam, it is positive. Any trace of yellow or orange colour denotes a negative reaction.

Prophylaxis. The prophylactic measures in enteric fevers consist in the prevention of dissemination of excreta from patients, convalescent or healthy carriers, so that they do not convey infection into the system of sewage disposal. Secondly, the disposal of infected sewage should be such as not to reach and contaminate the water supply or be accessible to flies. Where the disease is endemic, or during the period of an epidemic, special precautions should be taken to avoid all predisposing factors. Drinking water should always be boiled and special attention is necessary to ensure the purity of milk, butter or other food-stuff that might directly or indirectly be exposed to infection. Typhoid patients should be isolated as early as possible. The excreta must be disinfected, as well as all objects used by the patient, *viz.*, linen, utensils, thermometer, etc. The advent of prophylactic inoculation has greatly reduced the incidence of both typhoid and paratyphoid infections. Statistical evidence of the use of vaccine in epidemic and endemic areas shows that it considerably reduces the susceptibility of the individual to the disease and the case mortality shows a marked decrease after the use of this prophylactic inoculation. The vaccine which is generally known as T.A.B. vaccine, contains 1,000 million of typhoid bacilli, 500 millions each of paratyphoid A and B in each c.cm. Two doses of 0.5 and 1.0 c.cm. are given at an interval of about ten days. For details see vaccine therapy.

General management. Rest in bed, strictly regulated diet and good nursing are the principal points to be aimed at. The patient should be kept in a well ventilated room and confined to bed from the beginning of his illness. Intelligent and careful nursing is essential and all the specific instructions should be clearly written in the form of a chart and the condition recorded as it varies from day to day. The care of the mouth

is a matter of great importance. A combination of borax with glycerine is an efficient means of securing cleanliness of the mouth and gums ; a solution of sodium bicarbonate may be alternated with it to dissolve sticky mucus.

The idea underlying the treatment is to help elimination of the toxins from the body by the principal channels of excretion such as faeces, urine and sweat. With this end in view the treatment should be directed along the following lines :

Hydrotherapy. The use of water is of great importance. It may be utilised for sponging, tepid or cold, and a bath. Whenever the temperature rises above 103.5°F., the patient should be sponged with water at a temperature of about 70°F. About 15 to 20 minutes are necessary to sponge a patient efficiently. If a bath is required it should be given in a tub big enough to keep the patient under water except his head. The temperature of the water in the bath varies between 75 to 85°F., and the patient remains there for 10 to 15 minutes. The bath in most cases brings about distinct improvement in the condition ; it markedly lowers the temperature, brings about an improvement in circulation, lessens the excitability and helps in the elimination of toxins.

Diet. The importance of diet in the treatment of enteric fevers cannot be too strongly stressed. It should be nourishing and liberal in order to maintain the strength of the patient. A good deal of controversy exists over diet. Some give milk with the addition of a little quantity of sugar or cream while others give a much more liberal diet. It is to be understood that there is an increase of about 40 per cent. in the basal metabolism in enteric fevers with marked protein breakdown. This is due to the toxic decomposition of protein of the body and is not due to raised body temperature. Experimentally it has been shown that a large amount of carbohydrates with a moderate quantity of protein helps to maintain the patient in equilibrium ; protein diet alone fails to keep the body metabolism in equilibrium. If too much food is given there is likelihood of development of abdominal pain, discomfort, meteorism, haemorrhage or perforation. On the contrary, too little food will

starve the patient, delay convalescence and often the temperature will remain at a higher level until a larger quantity of food is given. The condition of the patient must be taken into consideration ; in a severe case it is difficult to give even a moderate quantity of milk without producing some discomfort, while a mild case requires more food.

In general, the diet given should have a caloric value of 2,000 to 2,500 calories, chiefly composed of carbohydrate and protein, the latter amounting to about 70 gm. in 24 hours. The proteins prevent excessive loss of weight, the carbohydrates give the necessary heat and energy and also oxidise the fats and thereby prevent acidosis.

The bulk of the food should be liquid, milk or its modifications, such as peptonised milk, malted milk, butter milk or whey are given. If there is diarrhoea and much fermentation in the intestine, the diet should be very simple and consist entirely of whey or glucose. Water may be given freely and as much as 3 to 4 litres of water should be consumed in a day. Barley water, lemonade, soda water are also useful. Glucose and lactose may be advantageously given frequently. An efficient drink can be prepared by the addition of some alkali such as bicarbonate of soda and lactose to water ; it should be given as often as the patient feels thirsty and is an efficient diuretic. See diet in disease, page 166.

Medicinal treatment. There is no specific drug treatment and medicinal treatment is indicated only to control symptoms and give the patient as much relief as possible. The various antiseptic drugs that have been tried intravenously do not seem to alter the course of the disease in any way ; the use of the intestinal antiseptics so as to alter the bacterial flora of the intestine is likewise without effect.

Abdominal pain and distension are often troublesome complications ; these are best treated with fomentations and turpentine stupes. Oil of cinnamon is recommended for the relief of such conditions and good results have followed its use in many cases. For meteorism, the rectal tube may be passed and a turpentine enema may be given. The diet should

at the same time be reduced and food should be liquid ; whey and albumen water should be substituted for milk and given at longer intervals.

Diarrhoea is due either to intestinal fermentation or to irritation caused by ulceration. It is, therefore, unwise to attempt to check diarrhoea so long as pain, distension and flatulence exist. As regards drugs, salol is largely used with a view to deodorizing the stools by inhibiting putrefaction and fermentation. But it is to be noted that intestinal antiseptics such as salol, beta-naphthol, chlorine mixture, etc., do not in any way alter the bacterial flora of the intestine. If the number of stools is very large, bismuth is useful either alone or in combination with Dover's powder. The amount of food should be reduced, and whey and albumen water in small amounts substituted for milk. Constipation occurs in many cases but it is unsafe to use purgative drugs to relieve it. In such cases an ordinary soap-water enema every alternate day or liquid paraffin may be given. For sleeplessness, see page 223.

A very serious strain is put on the heart and weakness of the cardiovascular system is obvious. Whatever be the immediate condition, the possibility of the heart being exhausted must be well recognised. In order to preserve the cardiac muscle from exhaustion, digitalis in the form of tincture should be given at the earliest evidence of myocardial weakness. With signs of failure of the circulation, strychnine (1/32 to 1/8 gr.) hypodermically or 1 c.cm. of camphor in ether or strophanthin (1/240 to 1/60 gr.) intravenously should be tried. See cardiac tonics, page 241.

Hexamine in doses of 10 gr. three times daily is largely used during the third week of enteric fevers. The antiseptic value of the drug especially in bacilluria which occurs between the second and the third week, is well recognised. Attendant complications such as cholecystitis, pyelitis and cystitis are also treated with large doses of hexamine.

The treatment of hæmorrhage requires the greatest care. Hæmorrhage is most likely to occur after the second week and

in the majority of cases a history of persistent diarrhoea may be traced. In hæmorrhage absolute rest is essential and an injection of morphine should be given. An ice-bag should be placed on the abdomen and food withheld for eight to twelve hours and the stools watched for blood. The use of normal horse serum (10 to 20 c.cm.) or hæmoplastin in 2 c.cm. doses is of proven value; calcium chloride 5 to 10 c.cm. of a 10 per cent. solution may be given intravenously; defibrinated blood in doses of 10 to 20 c.cm. given intramuscularly has also been used with success. In serious cases transfusion of blood may be necessary. There is no unanimity of opinion regarding the use of morphine. It is however the usual practice with many to give opiates by the mouth or an injection of morphine in order to give rest to the bowel and thereby check hæmorrhage. If perforation occurs, the only means of saving the life of the patient is by doing immediate laparotomy.

Serum treatment. See serum therapy, page 791.

Specific and non-specific vaccines: Conflicting results have been obtained with subcutaneous and even intravenous injections of typhoid vaccine in the treatment of the disease. The study of the records shows that this method of treatment is of doubtful value. Vaccine given for protection will not check an infection already installed and incubating, and likewise the statistical record of cases treated with vaccines does not show that this has a material advantage over other forms of treatment. Moreover in some cases it has been stated that the use of vaccines may predispose the patient to hæmorrhage. For specific vaccine treatment see vaccine therapy, page 773.

Non-specific vaccines have been tried in enteric fever and are said to have given good results in many cases especially those complicated with bone lesions. The treatment consists in giving intravenously foreign proteins, *e.g.*, *Bact. coli* vaccine in doses of 10 to 20 million organisms per c.cm. A reaction is produced which is characterised by fever, chill and leucocytosis after an injection. In no case should the vaccine used be old and stored for a long time. Whenever possible freshly pre-

pared vaccines should be given a trial as early in the course of the disease as possible.

Bacteriophage. The value of the administration of bacteriophage in the treatment of enteric fevers has not as yet been established. *In vitro* lytic principles may be obtained which have a marked effect on *Bact. typhosum*. It is therefore preferable if possible to obtain phage that will lyse the specific bacteria. The doses are 2 c.cm. every four hours for five or six days. It can be similarly employed as a prophylactic during an epidemic. See also bacteriophage therapy, page 808.

Convalescence. The management of the period of convalescence is very important. The diet should be gradually increased, and it is best to wait for a week or ten days after the temperature is normal before resorting to solids. The patient should be allowed to get up gradually; all strain and over-exertion are to be avoided. Constipation is to be particularly avoided and it is best treated by liquid paraffin and enemas. After an attack of typhoid fever the patient should have, if possible, a period of rest in the country or to some health resort before returning to his ordinary mode of life.

The treatment of typhoid carriers presents innumerable difficulties. In such cases hexamine should be given continually in large doses. Autogenous vaccines offer a good chance of success for the treatment of these carriers; particular care should be taken to dispose of their urine and fæces and they should not be allowed to handle food.

BACILLARY DYSENTERY

Bacillary dysentery occurs over the whole world but is more common in the tropics, and may become epidemic when conditions such as over-crowding and bad sanitation exist. Infected persons and carriers are mainly responsible for its spread. Infection may be direct or through contamination of food and water. Milk is one of the common articles of diet implicated and flies play an important part in the spread of the disease. The incidence of the disease is at its minimum in the cold weather, and increases when the hot weather sets in.

Recent work has shown that bacillary dysentery is far more common than the amœbic form, even in tropical climates.

There are two main types of the disease:—

(a) *Bacillary dysentery due to non-mannite-fermenting bacilli of the Shiga type.* In these cases collapse may be present and pyrexia is usually marked. The stools are very frequent, 16 or more a day, but may vary from none at all, in the acute gangrenous type with paralysis of the gut, to the incessant passage of stools resembling the rice water stools of cholera, but containing flakes of blood-stained mucus. The Shiga bacillus produces both an intracellular and an extracellular toxin, and also produces poisonous pressor bases from animal proteins.

(b) *Bacillary dysentery due to mannite-fermenting bacilli of the Flexner group.* In these cases collapse does not occur as a rule, pyrexia is less marked, and the stools are usually less than 16 a day. The blood and mucus in the stool may not be visible to the naked eye, and many cases present the symptoms of mucous diarrhoea, the stools being faecal-coloured or pale. The so-called 'hill diarrhoea' is usually due to infection with a bacillus of the Flexner group. This group of bacilli produces an intracellular, but no extracellular toxin. They produce indol and ferment carbohydrates but do not ferment lactose.

The cases of bacillary dysentery range in severity from very mild to fulminating choleraic types. The onset is usually sudden with rise in temperature, abdominal pains, tenesmus and diarrhoea with blood and mucus in the stools. In severe cases there are marked symptoms of toxæmia and dehydration. The colon and the lower part of the ileum are inflamed and there may be ulceration. The isolation of the dysentery bacilli is the most reliable method of diagnosis. Stools containing no mucus very rarely yield positive results; these should therefore not be selected for examination. If the material has to be sent any distance an equal quantity of Teague's solution should be added and the material kept in a cool place. It is only in the first seven days of the acute attack that positive bacteriological results are possible. In chronic bacillary dysentery it is difficult to isolate the causative organisms and repeated examination of the stool is necessary.

Agglutinins develop in the blood of dysentery cases usually after seven days from the onset. Positive agglutination in a dilution of 1 in 25 in Shiga infection, and of 1 in 50 or over in Flexner, are highly suggestive of recent infection. Carriers have been detected by their blood agglutinating dysentery bacilli. A cutaneous reaction on the lines of the Schick test for immunity to diphtheria has been described. Cellular exudates and macrophage cells in the stools are helpful in diagnosis. In early acute bacillary dysentery there are numerous desquamated epithelial cells and degenerated polymorphonuclear cells. Columnar epithelial cells are more numerous than in amœbic dysentery.

in which the cells are mainly mononuclear leucocytes with well defined nucleus.

Carriers. Healthy carriers particularly of the Flexner group of organisms do exist. The carriers of Shiga bacilli are usually persons who are ill.

Bacillary dysentery occurs very frequently in children and young adults. It prevailed on all fronts during the War. In many countries bacillary dysentery comes in severe epidemics and is responsible for a high case mortality which may range between 2 to 80 per cent. The Shiga bacillus is much more toxic than the organisms of Flexner group. The Shiga toxins have been shown to act on the central nervous system of rabbits. The high degree of toxicity of Shiga's bacillus has militated against the successful use of vaccines made from it. Anti-toxins have been prepared which given subcutaneously have proved invaluable, and prophylactic vaccination with an active anatoxin prepared from a very toxic strain against bacillary dysentery (Shiga type) has been tried with some degree of success.

Treatment of Acute Bacillary Dysentery

General measures. The first and the most important principle in treatment is to place the patient at absolute rest in bed. The ulcers in the gut will take ten days or so to heal. If the patient is not kept in bed the condition frequently becomes chronic in type, and this is especially the case with mild infections due to the bacillus of Flexner, where the patient only has a mucoid diarrhoea for a few days and neglects proper treatment of the condition.

Warmth is of importance in the treatment of bacillary dysentery, especially where there is tendency to collapse and a hot water bottle applied to the abdomen is often very helpful.

Diet is important, foods leaving coarse residue should not be given. In Shiga infection, thin gruels like barley-water and rice-water should be given and all animal proteins eliminated from the diet, as this measure will materially help in reducing toxæmia. The diet should consist solely of carbohydrates, such as arrowroot, barley-water, glucose feeds, tea or coffee with very little or no milk. These cases do not tolerate milk well as a rule, but when the temperature has come down to normal and the stools are well-formed, milk and finally pro-

teins may be gradually added to the diet. In Flexner bacillus infections, on the other hand, carbohydrates should be eliminated from the diet, and such articles as meat extracts, chicken broth, citrated milk, jellies, weak beef tea, and later eggs, should be given. During convalescence fish and meat may be gradually added to the diet, but carbohydrates should be added last of all. Many of these patients show intolerance to carbohydrates for a long time. In both groups of cases the food should be given slightly warmed, and in small quantities at a time as cold drinks are apt to increase intestinal peristalsis. A return to full diet should be very gradual during convalescence as any dietary indiscretion may lead to relapse.

Medicinal treatment. *Cathartics.* The purgative treatment still maintains its position, the idea being to lessen the absorption of toxins by washing out the bowels. There is no other line of medicinal treatment for bacillary dysentery so satisfactory and so simple as the use of magnesium sulphate and sodium sulphate in small doses repeated frequently. The loss of a day or two in starting the administration of salts will greatly prolong the convalescence of the patient by allowing time for the toxins to produce ulceration before the congestion of the large bowel is relieved. As a preliminary purge a full dose (1 oz.) of the following is given:—Sodium sulphate 2 dr. magnesium sulphate 2 dr., tincture of ginger 5 min. and peppermint water 1 oz. This is followed by 2 dr. doses of the above mixture every hour until free watery stools are passed, when the same dose may be given at six-hourly intervals till the stools are feculant and free from blood and mucus. An initial dose of castor oil with or without a little tincture of opium as indicated may be given in early phases of the disease instead of the initial saline purge.

In severe cases administration of normal saline is advised to prevent dehydration, 300 to 500 c.cm. may be injected intravenously or subcutaneously. A 10 to 25 per cent. solution of glucose intravenously in severe cases supplies nourishment and fluid and 1/100 gr. (0.6 mgm.) of atropine sulphate checks pain and tenesmus. Burkett (1921) used

Turkey rhubarb in half a teaspoonful doses every one to three hours until the drug appeared in the stool ; for children 5 gr. doses were given every 2 or 3 hours. Calomel should not be given.

Adsorbants. Kaolin and charcoal are said to adsorb toxins. Kaolin is given in suspension and as much as 300 gm. may be necessary in the course of a day, stirred up in a pint of hot tea. Charcoal in doses of 80 gm. per day may also be used, animal charcoal being preferred to the vegetable. (See also page 413.)

Bismuth is often very valuable in severe cases, associated with purging ; the carbonate is probably a better preparation to use than the subnitrate, as the latter is apt to contain impurities ; a dose of 1 or 2 dr. may be given suspended in half a tumblerful of water or soda water every 4 to 6 hours until the stools become black.

Lactose. Sugar of milk has been recommended with the idea that it inhibits the growth of dysentery bacilli and favours the growth of acid-forming bacteria. It is given in doses of two dr. 3 or 4 times a day when it acts like a saline purgative. It is particularly useful in chronic dysentery.

The routine use of opium in the treatment of dysentery is to be most strongly condemned. In many cases, however, where the patient is worn out with the constant tenesmus and pain and cannot obtain sleep, $\frac{1}{4}$ gr. of morphia may be given hypodermically at night. The resulting rest and sleep will materially help the patient in his fight against the disease. A good working rule is that if the patient has had no sleep for two nights, and the temperature is falling, $\frac{1}{4}$ gr. of morphia with $\frac{1}{100}$ gr. of atropine may be given.

Bacteriophage. It is in cases of acute bacillary dysentery particularly due to Shiga bacillus that bacteriophage therapy has given good results. In some patients treated with bacteriophage the symptoms disappear in a day or two and the patient becomes convalescent. It is important that bacteriophages possessing a high virulence for the local strains of dysentery bacilli be employed and that it be administered early in the

disease. It must be remembered that bacteriophage attacks the bacilli present in the gut, thus rendering them incapable of causing further damage, but it cannot directly repair the damage already done or neutralise the toxins already formed. It is important, therefore, that along with the administration of bacteriophage other modes of treatment which are calculated to bring about the elimination of toxins and the healing of the ulcers should be employed. For details see bacteriophage therapy, page 808.

Chronic Dysentery

The successful treatment of these cases entirely depends upon making a most careful assessment of the conditions and factors present and in securing the confidence and co-operation of the patient. Persistence and patience are necessary from the patient as well as the doctor.

Milk is a very suitable diet in the early stages, but unfortunately so many of these patients have been kept for long periods entirely on this diet that the sight of milk nauseates them. A diet consisting mainly of proteins such as soups, jellies, eggs and the juice of fresh fruits with later additions of boiled fish, minced chicken, etc. is recommended. The carbohydrates are added last of all to the diet.

A thorough overhaul of the digestive system is made. The teeth are examined for pyorrhoea or absence of molars and any defect corrected. Repeated examinations of the stools must be made until the causative organism is isolated.

In the chronic relapsing type of bacillary dysentery, little advance has been made so far as the drug treatment is concerned. Henry and Brown (1923) found *Mansonia ovata*, *Rhynchosia adenodes*, *Burcis abyssinica* and *B. sumatrana* useful. They all contain tannin. *H. antidyenterica* is also used and probably owes its action to the alkaloids it contains. In persistent extensive ulceration with secondary infection and toxic absorption which do not yield to medicinal treatment surgical treatment may be required. Rest and careful dietary measures are most important. Bowel washes are useful in cases with extensive

ulceration of the lower gut. Rogers recommends 1 to 1½ pints of olbargin solution in strength of 1 in 5,000.

Serum treatment is useless here and vaccines have been extensively tried. Some clinicians are very enthusiastic about vaccine treatment. Where possible, autogenous vaccines should be employed. See vaccine therapy, page 773.

Bacteriophage treatment acts in a most remarkable manner in some cases while it produces no effect in others. It is particularly useful where previous examination in the laboratory has shown that the causative organism is lysable by the bacteriophage. If necessary, bacteriophage can be grown on the causative organism and then administered to the patient.

Bact. pseudo-carolinus Infection

In a large number of cases of subacute and chronic dysentery in the tropics *Bact. pseudocarolinus* can be isolated from the stool. This has been suggested as a phage-mutant form of *Bact. flexner*. Although definite proof of the pathogenicity of this bacillus is lacking, it is probable that its presence in the gut gives rise to a train of symptoms which are not met with in other intestinal infections commonly encountered in Calcutta. The association of the bacillus with chronic infection with *E. histolytica*, hookworm, etc., has been observed. The common symptoms complained of are alternate constipation with diarrhoea with occasional passage of mucus in the stool. Whether the bacillus is responsible for the production of these symptoms, is difficult to say at present. When the stools contain blood and mucus salines improve the condition; any associated conditions should also be treated. Later on a course of 6 injections of autogenous vaccines should be given beginning with 10 million organisms and increasing up to 40 millions or more according to reaction; calcium and parathyroid should be given by the month.

CHRONIC ULCERATIVE COLITIS

Ulcerative colitis was described as early as 1875 though it was at that time indistinguishable from bacillary dysentery. It has now come to be recognised as a distinct clinical entity. It begins as an acute inflammation of the mucous membrane of the colon, leading to patches of localised necrosis, followed by separation of sloughs and superficial ulceration. If the ulcers heal, ragged polypoidal masses of mucous membrane remain which may sometimes lead to fibrosis and stricture.

Many workers consider that ulcerative colitis develops as a result of infection with one of the dysentery group of organisms. Dudgeon (1923) isolated Flexner's bacillus from material obtained from the surface of an ulcer in two cases of ulcerative colitis. Hadfield (1927) isolated it from a swab from such an ulcer. Tholaksen and Cadman (1928) cultivated the bacillus from the material obtained by scraping the base of an ulcer. The claim that the disease is due to the dysentery organisms is, however, discounted by many investigators.

Bargen (1928) isolated a diplococcus from the ulcers which he regarded as the cause of the disease. Although intravenous injections of rabbits with Bargen's diplococcus cause diarrhoea with blood and mucus, the experimental disease does not resemble human ulcerative colitis.

Entamoeba histolytica has also been regarded as a causative agent though this has not been confirmed by laboratory and other evidence.

Patients suffering from ulcerative colitis are often met with in the tropics. In India quite a number of cases occur in which neither *E. histolytica* nor any of the dysentery group of bacilli can be isolated, and the symptoms are very similar to those occurring in this condition.

Treatment. In treatment, certain general principles should be followed. Rest in bed, warmth and a generous mixed diet are essential. Too much restriction in the dietary is injudicious. The main principle in this direction is avoidance of cellulose-bearing fruits and vegetables and the omission from the food of such articles as may give rise to flatulence. In acute cases, liquids of high caloric value are preferable, and the diet is increased with the progress of the case towards recovery. In chronic cases, a high calorie, high vitamin and relatively low residue diet is recommended.

A great variety of drugs has been given by the mouth, main reliance being placed on bismuth salts, tannic acid compounds, kaolin and the opium derivatives. All these medications have a distinct place so far as the relief of symptoms is concerned without having any specific effect on the disease. Large doses of bismuth (a teaspoonful every 2 hours) or kaolin or 'bolus alba,' cause an amelioration of diarrhoea, with relief from the constant distressing urge to go to stool. As a sedative to intestinal hyper-peristalsis, opium is a useful drug (in the form of tincture of opium in small doses); it undoubtedly gives relief when there is excessive fermentation in the intestine. Injections of morphine to relieve this so-called 'gas' pain should

be avoided. Charcoal by absorbing gases from the intestine may relieve the patient of discomfort.

Hurst (1931) strongly advocated the use of antidysenteric serum. Recovery has been seen only in early cases, and in a very large number of cases no definite improvement is noticed and relapses after antidysenteric serum treatment are quite frequent. Bergen (1928) advocated the immunisation of the patient against the causative organism which he considered to be a diplococcus. In chronic cases repeated graduated doses of diplococcus vaccine have been administered subcutaneously. Such treatment is usually given for over a month. Though the treatment may be beneficial in certain cases, success has not been uniform. Many workers have failed to isolate Bergen's diplococcus in a large proportion of cases. Repeated serial bacteriological examination of the stool should be carried out and an autogenous vaccine prepared from any pathogenic organism found.

In a condition that is essentially a local ulcerative lesion of the colon, colonic irrigations with antiseptics and astringents are useful. But in the acute or in the early stages of the disease medicated enemas should be forbidden. Irrigation of the colon when done carefully, promotes drainage, removes products of infection, prevents absorption of toxic material and makes the patient comfortable. For this purpose, innumerable substances in the form of aqueous solution have been used. Silver salts, potassium permanganate, zinc sulphate and iodine, have all been tried. Neutral acriflavine in strength of 1 in 4,000 aqueous or saline solution has given satisfactory results. To begin with, 750 c.cm. of the solution is given twice a day and retained each time from ten to twenty minutes. Later, it may be administered on alternate days using a weak solution of sodium bicarbonate (0.5 per cent.) on the intervening days. The treatment is continued until the temperature is normal, diarrhoea has ceased, and the sigmoidoscopic and proctoscopic examination reveal the disappearance of all ulcerative lesions. Tannic acid (1 to 2 gr. in an ounce) is also a useful drug; after a preliminary lavage with normal saline solution. Tidy (1931) recommends

the following procedure for rectal medications: (1) starch and opium enema, (2) colonic washes, and (3) in later stages medicated enemas. He uses a starch and opium enema (3 oz. of mucilage of starch with 20 to 30 min. of tincture of opium) at the outset; this should be given not more than five times a week and never more than on three consecutive days. The course is continued till there are not more than five stools a day. The colonic wash consists in giving two pints of normal saline every other day and continued until the stools are less than five a day. The medicated enema is used only when the stools number less than five a day; about 20 gr. of albargin in 25 oz. of water is administered. This should not be used for more than three times a week and at least there must be a week's interval between the courses.

The after treatment of the disease requires some consideration. There is always a tendency to relapse and the treatment has often to be continued for long periods. Such associated conditions as oral and pharyngeal infections and anal complications must be treated, as relapse may follow an acute sore throat or development of an anal abscess. Diarrhoea or constipation may give trouble. Looseness of the bowels may continue for some time and may respond to starch and opium enema and colonic washes. Constipation is relieved by liquid paraffin. Surgical treatment has been advised and appendicostomy is said to be useful in some cases but opinions differ as regards its efficacy and its superiority over medical treatment.

The use of diathermy has been advocated, the active cathode being placed in the rectum, the inactive being applied round the waist. The greatest concentration of the current occurs in the rectal and sigmoid regions and the treatment is usually given for twenty minutes at a time. The result of diathermic current is to cause internal heating and improved lymph and blood circulation of the colon. Ionization treatment has also been applied in cases of ulcerative colitis. Treatment is generally given for fifteen minutes and repeated once or twice a week.

COLIFORM INFECTION

At a very early stage *Bacterium coli* appears in the intestine of the infant and throughout life man carries these germs in his colon. In health *Bact. coli* is confined to the large intestine or at any rate does not extend far beyond the ileocaecal valve into the small intestine.

Normally, barriers exist against the escape of organisms into the lymphatics or blood stream and these are:—(1) The intact intestinal epithelium, (2) mucus secretion and (3) the lymphoid tissue found in the intestinal wall and the lymphatic glands which lie in relation to the ileocolic vessels. But conditions which disturb the above protective mechanism and facilitate the escape of bacteria may be set up (1) by disease of the bowel of which chronic intestinal stasis is the most common, or by abdominal operation, and (2) by treatment, of which the most frequent is violent purgation.

Of the intestinal affections, those showing signs of irritation of the mucous membrane, *e.g.*, colitis, chronic diarrhoea, diverticulitis seem more prone to give rise to urinary infection than atonic states of the colon with simple constipation. Intestinal infection, when it is complicated is specially liable to extend to two organs, *i.e.*, the gall bladder setting up infective cholecystitis, and the urinary tract, giving rise to pyelitis and cystitis. Urinary stasis secondary to urinary calculus, strictures, enlarged prostate, gravid uterus, etc., may also be contributory factors. The coliform organisms reach the pelvis of the kidney and the bladder by the urethra as well as by the blood stream. Dudgeon, Wordley and Bawtree (1921) discuss the question of mode of infection with *Bact. coli* in the light of their own findings and those of others, and are inclined to believe that in the male infected with a hæmolytic *Bact. coli* the route of infection is from the intestine into the blood-stream either direct or by the lymphatics. In the female probably the infection is more commonly along the urethra. Of later work on the question that of Vincent (1925) points to the hæmic route of infection. *Bact. coli* may cause a primary pyelitis and cystitis but occasionally the reverse is the case. In the pelvis of the kidney there is a catarrhal inflammation extending on to the papillæ and in some cases foci of suppuration may occur in the kidney substance. The symptom of coliform infection of the urinary tract are pain and frequency of micturition and usually a rise of temperature. Not infrequently there are rigors and the patient is acutely ill. The urine is strongly acid and contains numerous pus cells. *Bact. coli* is easily isolated on culture. In cystitis if a blood culture is made during a rigor *Bact. coli* may be isolated. Cabot and Crabtree (1916) obtained positive blood cultures in 40 per cent. of their 32 cases under these circumstances. Whether such bacilli gained

access to the blood from the intestine or from the bladder lesion is undecided.

Another diseased condition associated with *Bact. coli* is cholecystitis. In such cases *Bact. coli* cannot be cultivated from the blood unless abscesses are present in the internal organs. Possett (1927) from a review of the literature of the action of *Bact. coli* in cholangitis and cholecystitis concluded that infection passes to the liver directly from the intestine and not by the blood-stream. Moynihan (1927) believed that the peritoneal coat of the gall bladder is first infected presumably from *Bact. coli* that have passed from the intestine into the peritoneal cavity. The infection of *Bact. coli* into the healthy bladder or gall bladder does not cause an infection in animals but such a condition ensues if the bile duct or urethra is obstructed. Hurst showed that the colon bacillus can grow in the duodenum and stomach if no hydrochloric acid is secreted and at the same time the movement of the stomach is inhibited. Such a condition always favours retrograde infection. It therefore seems probable that any abnormality which interfered with drainage from the gall bladder and any extraneous focus of infection, e.g., appendix, assist in the production of cholecystitis.

Septicæmia due to *Bact. coli* is very rare, but it may be found when there is a focus of suppuration, e.g., abscess in the liver, or during rigor in cystitis, or in acute infective processes. In new-born children a fatal condition known as Winckl's disease is a hæmorrhagic septicæmia produced by *Bact. coli* (Felly and Keefer, 1924).

Whether *Bact. coli* or its products can on ingestion cause diarrhoea is still uncertain. In young infants it is very probable that gastro-enteritis may be caused by changes produced in cow's milk by many bacteria, including *Bact. coli*. The intestine of an individual and the strains of *Bact. coli* in it appear to become adapted to each other and, if there is want of such harmony, symptoms are at once produced. It is possible that foreign strains of *Bact. coli* when swallowed may cause gastro-intestinal disturbance. The problem of the causation of diarrhoea in infants and as to how far *Bact. coli* is to be incriminated is far from being settled.

Bact. coli probably does not pass through the healthy bowel into the peritoneal cavity, but when the bowel is damaged by trauma or strangulation such passage occurs giving rise to peritonitis. It is sometimes found as the sole infecting agent in abscesses found in the region of the anus and urethra.

Treatment of urinary infection with coliform organisms. In the acute stage the patient must be kept in bed so as to ensure rest and warmth. Even in the chronic stage it is important to avoid cold and fatigue. As the bowel is the source of nearly all the infections, it must be carefully attended to.

A good initial purgative should be given and then the bowel should be kept open daily with cascara; some advise liquid paraffin and agar along with high colon lavage. Suitable diet is of great importance. Too much milk must not be given, but the patient should take plenty of fluid (6 to 8 pints daily). Diet should be low in total protein content; meat, eggs, and raw milk are excluded entirely, junket, whey, butter-milk and cream being allowed. Rice, bread, honey, butter, porridge, vegetables, fish and chicken are gradually allowed when the acute symptoms have subsided.

Intestinal antiseptics have been recommended but it is doubtful whether they are of any value. A cachet containing salol 10 gr., grey powder $\frac{1}{2}$ gr., with water between meals two or three times daily is said to be useful.

In acute cases with pyrexia, full doses of alkalis are very helpful and should be continued until the urine has been rendered alkaline for 3 or 4 days. A mixture of sodium bicarbonate 30 gr., sodium citrate 30 gr., potassium acetate 30 gr., syrup of orange $\frac{1}{2}$ dr. and water 1 oz., is given four-hourly. As soon as the urine is alkaline the temperature usually falls and the mixture can later be given six-hourly and then three times a day or as required. Hexamine in 10 gr. doses in a glass of water should now be given three times a day before food. After the food a mixture containing acid sodium phosphate 30 gr., tincture of hyoscyamus $\frac{1}{2}$ dr., and chloroform water up to 1 oz. is given. The alkaline and acid treatment should be alternated every 3 days. It is well to change the hexamine for one or other of its derivatives, *e.g.*, cystopurin, helmitol, etc., every now and then. Urotropine may be given intravenously in doses of 2 to 5 c.cm. of a 40 per cent. solution. Acriflavine and mercurochrome have also been used intravenously with beneficial results. Neoarsphenamine in doses of 0.15 to 0.30 gm. intravenously every five or six days has been used with success. Hexyl-resorcinol is another drug that is often used in urinary infections. To obtain satisfactory results, the dose should not be less than 0.45 to 0.6 gm. three times a day, *i.e.* from 3 to 4 capsules after each meal; fluids should be restricted and sodium bicarbonate should not be given

at the same time. This treatment has to be continued for 2 to 3 months. Other drugs, *e.g.*, colloidal silver preparations, methylene blue, pyridium and methenamine, have been tried. Gutzeit (1931) recommended uricedan in doses of one or two teaspoonfuls well diluted two or three times a day. Irrigation of the bladder with antiseptic lotions, *e.g.*, acriflavine, mercurochrome, Condy's lotion, etc. is used in suitable cases.

Lepoutre (1930) reported excellent results with a serum prepared by injecting horses with *Bact. coli* of urinary origin. Non-specific therapy has been tried without effect. Benefit has followed the use of bacteriophage of which a strain must be employed which has a high lytic power towards the invading organism; 2 to 3 c.cm. are injected subcutaneously every other day till 4 doses are given. At the same time 10 to 20 c.cm. are given by mouth, and a like amount injected into the bladder to be retained as long as possible. While this treatment is being given, the urine should be kept alkaline and no antiseptics should be given. Autogenous vaccines are given after the acute symptoms have subsided and the results are on the whole very satisfactory. At the same time the stools should be examined and any pathogenic organism isolated included in the vaccine. Infection of the intestines by protozoa or helminths should receive appropriate treatment.

Many cases of chronic coliform infections of the urine prove very resistant to any form of drug treatment. The introduction of ketogenic diet treatment constitutes an advance. It is based on the observations that the urine of patients suffering from diabetes with ketoneuria and of patients treated with ketogenic diet for epilepsy does not putrefy on standing for several days in a warm room. Presumably the urine contains some substance which prevents the multiplication of micro-organisms. Shohl and Janney (1917) showed that when the reaction becomes acid, with a pH of 5 to 4.6, the growth of *Bact. coli* is inhibited.

The ketogenic diet in the treatment of pyelitis was first introduced by Helmholtz and Clark in 1931. Though they showed that the diet produced some change in the urine which makes it inhibit the growth of bacteria, the precise manner of

its action was not determined. All workers now agree that the change in reaction of the urine is not the only factor causing inhibition of the growth. Ketonic urine inhibits the growth of *Bact. coli* to a much greater extent than normal urine rendered acid to the same degree by the use of acidifying salts. Clark (1932) expressed the opinion that the growth-inhibiting effect is due to the presence of some bactericidal substance excreted. Dick (1932) showed that a ketogenic urine inhibits bacterial growth even when the reaction of urine has a pH of 5.5 or is more alkaline. Fuller (1933) states that bacterial growth in the urine is inhibited chiefly by 1- β -oxybutyric acid, which is excreted after ketogenic diet and that the activity of this substance increases in proportion to the acidity of urine. The clinical application of ketogenic diets in *Bact. coli* infections has been worked out by various workers. The treatment consists of giving diet which will produce ketosis, and if the pH does not fall below 5, ammonium nitrate or chloride is given in doses of 0.5 gm. three times a day. The ketogenic diet contains a preponderance of fats over carbohydrates and proteins. It is usually necessary to use a diet with a ratio of 3 : 1, i.e., F=3 (C+P). If this diet does not produce ketosis then the carbohydrates may be reduced by 5 gm. every three days. Ordinarily a ketogenic diet consists of protein 60 gm., carbohydrate 20 gm., and fat 240 gm. A normal amount of fluid (2 to 3 pints) is taken in the form of water, and it is essential that no other food is taken. The urine should be tested daily for pH value and ketone bodies, and the result of treatment judged by cultures of the urine.

In some cases this diet may fail to maintain this standard of urinary ketosis. It has been suggested that ammonium chloride in daily doses of 125 gr., in addition to other measures, may bring down the pH to 5. Poulton observed that he found a more marked ketosis if more protein was given in the diet, and he advises an alternative method by giving calcium chloride in doses of 7½ gr. daily.

CHOLERA

Cholera is an acute specific gastro-intestinal affection caused by *Vibrio cholerae* discovered by Koch in 1883. The organism

primarily multiplies in the lower portion of the ileum. The symptoms are vomiting, profuse and effortless diarrhoea, muscular cramps, collapse and suppression of urine. The disease may run a course of a few hours to a few days. The clinical course of the disease is divided into a stage of evacuation in which there is great loss of fluid from the body through repeated profuse discharge of rice-water stools and copious vomiting. Following this is the collapse stage, with signs of failure of circulation, an almost imperceptible pulse, hoarse whispering voice, cold clammy skin, subnormal axillary temperature, shrivelled and cyanotic extremities and anuria. Muscular cramps, which usually commence in the first stage, get most severe during this stage. The most dreaded and frequent complication of cholera is continued suppression of urine, death with uræmic symptoms inevitably following if the condition is not relieved within two or three days. Next to suppression of urine, the most frequent and fatal complication is pneumonia which may be difficult to diagnose during life. Suppurative parotitis occurs in about 1 per cent. of cases. In severe cases in asthenic subjects sloughing of the lower half of cornea, bed-sores or gangrene of a limb may ensue. Sudden heart failure may supervene during convalescence, if the patient is allowed to be up and about too soon. Usually a condition known as the stage of reaction may supervene on the algid stage, a febrile condition of greater or less severity may develop. Hyperpyrexia is an occasional though rare occurrence in cholera, the temperature rising to 107°F. These cases are almost invariably fatal. Convalescence is comparatively rapid considering the great severity of the disease.

India is considered to be one of the chief sources of infection of cholera. It is endemic in the delta of the Ganges and the various world-wide epidemics can be traced to that source. Though it is customary to speak of Lower Bengal as the home of cholera, it is by no means certain that other Eastern localities, *viz.*, Bangkok, Canton, Shanghai, etc., have not some claim to similar distinction. Only in such countries as Siam, India, China, the Philippines, Indo-China, where large proportion of the populations still consume water from rivers, shallow wells, tanks, ponds, creeks, does the menace of cholera persist. There is some vague reference to this disease, in ancient Greek litera-

ture. *Susruta* in India, in the 7th century A. D. described a disease with symptoms and signs of typical attacks of cholera. Detailed accounts of this disease in India were published by the Portuguese, Dutch and English physicians during the 15th, 16th, 17th and 18th centuries. It was thought that cholera did not exist in China before the 19th century and its early occurrence is stoutly denied by many investigators. During the pandemic of 1817 the infection invaded China by the land route from India. In 1830 cholera visited Europe for the first time and since then there have been at least five epidemics, *i.e.*, 1848-51, 1851-55, 1865-74, 1884-86 and 1892-95. Great Britain had been involved seriously in four of these epidemics, *i.e.*, in 1832, 1848, 1854-55 and in 1866. The 1870-73 epidemic spared Great Britain, but it crossed the Atlantic and spread in the United States.

During the great pandemic of 1883 Koch at the head of a German commission took up investigation of the disease in Egypt but soon after his arrival in Alexandria the epidemic there came to an end and Koch came on to India. It was in the Medical College Hospital, Calcutta, that after a study of 42 cases of cholera and 28 autopsies Koch in the winter of 1883-84 worked out completely the aetiology of the disease, and in his report at the first conference on cholera held in Berlin in 1884 Koch gave an account of the organism which has been but little altered by the work of the last fifty years. Koch definitely established that the organism now known as *Vibrio cholerae* is the cause of cholera. At first there was considerable opposition to the acceptance of Koch's conclusion and this opposition was strengthened by the finding of vibrios in places where there was no cholera. A considerable controversy on the significance of these vibrios started in 1884 just a year after Koch's discovery of the organism and has been in existence for nearly half a century.

The typical forms of cholera vibrio present a quite characteristic aspect and appearing as Mackie puts it as short definitely curved cylindrical organisms, with round or slightly tapering ends and measuring usually 1.5 to 2 μ in length by 0.3 to 0.4 μ in breadth. Vibrios kept under more or less unsuitable conditions may show marked atypical forms. A variety of shapes may be met with, *e.g.*, straight organisms, thicker and swollen individuals, spherical forms with faintly stained centres, spindle-, club-, and pear-shaped organisms, individuals with irregular swellings, long swollen spirals measuring upto 17 μ and cells which present a completely distorted structure. Recently, a filtrable stage of the cholera vibrio has been claimed. Pasricha, de Monte and Gupta distinguish a G-type small coccal form which are filter-passers and later develop into vibrios. They admit that the aetiological importance of this form is not yet established.

The organisms grow well in alkaline media; the oldest and still the most commonly used of these is a 1 per cent. alkaline solution

of peptone water. When grown in peptone water the organism gives what is known as cholera-red reaction on addition of pure sulphuric acid. Interesting as this reaction is, its practical importance is limited. This reaction is not specific and certain cholera-like vibrios and other micro-organisms also give rise to this reaction. Serological reactions occur and they are important for the identification of vibrios.

The cholera vibrio can also be identified by an agglutination test with a specific anti-cholera serum. Greig (1919) showed that in the early part of the season the vibrios nearly all agglutinated in high dilutions of the serum, but towards the end a few non-agglutinating vibrios were met with. These latter organisms are regarded by some as *para-cholera* vibrios. Tomb and Maitra (1925) have revived the old theory that non-agglutinating vibrios may become pathogenic and produce outbreaks of cholera. Pasricha and his co-workers (1931) in a study of the changes induced in the serological reaction of cholera-like vibrios under the influence of bacteriophage, concluded that there is some bacteriophagic and serological relationship between the true cholera vibrio and the cholera-like vibrios. Although there are many vibrios that have no relationship with the true cholera vibrio, a large percentage of vibrios that are isolated in nature in places where cholera exists, are mutation forms of the true cholera vibrio and undoubtedly play a great part in the aetiology of the disease.

It has not as yet been definitely established whether an exo- or endo-toxin elaborated by the living vibrio is of exclusive importance in the production of the symptom. Kolle and Prigge, however, made a strong case for the endo-toxin theory. Suckling rabbits up to nine days can be infected orally (Metchnikoff) but Sanarelli has shown that there is enough acid in their gastric juice to prevent the passage of vibrios into the intestines.

Apparently healthy persons, usually after contact with cholera cases, may pass vibrios in their stool and thus be a source of infection to others. Dunbar was the first to demonstrate the presence of cholera vibrios in the faeces of apparently healthy persons. Experimentally, Greig has shown that intravenous injection of cholera vibrios may produce infection of the gall bladder in guinea-pigs. In man the vibrios have not been recovered from the blood, but they have been found frequently in the gall bladder which is sometimes inflamed in fatal cases of cholera. Such persons may become cholera carriers but only a small percentage of cases pass vibrios for more than 3 to 4 weeks.

Formerly it was held that the method of transmission was exclusively by water and food supply with a certain consideration of dangers from fomites especially to that connected with clothing soiled by the cholera discharge. Dissemination by human beings is the most important factor in cholera epidemiology. Cholera follows the great routes of human intercourse. In India during the religious gatherings, people are collected together in large numbers and under highly

insanitary conditions; cholera breaks out among them and when they separate and proceed homewards they carry the disease along with them, infecting the people of the places they pass through. Cholera never travels faster than man; but in modern times owing to increased speed of locomotion epidemics advance more rapidly and follow a more erratic course than they did years ago. It always follows the lines of communication by river, road, rail or ship. Although it travels along the trade routes, it never advances far unless along its path there are places where sanitary conditions are such as will help the disease to take root and start afresh.

All the facts in connection with the spread of cholera by land or water can be best explained by cholera carriers. The individual who is excreting vibrios while in apparent health, is far more dangerous than the one who is a well-recognised case of the disease. There are three categories of carriers—the incubatory, convalescent and the healthy, of which the first one is certainly dangerous. The last two do not represent permanent reservoirs of infection as is the case in other infectious diseases. Water supplies or food contaminated by dejecta from cholera patients or carriers are also dangerous. Milk is a splendid culture medium for the cholera vibrio, and many widespread epidemics have been traced to milk infection. The common house-fly and other insects play an important part in the spread mechanically, by settling on articles of food after having been in contact with infected materials.

Laboratory diagnosis. The organisms can be found in the faeces and the vomit early in the disease, and begins to disappear from the fourth to the fourteenth day. In examining a specimen a dried film is prepared and stained by Gram's method, the vibrios can be identified as Gram-negative comma-shaped organisms. The faeces should be cultivated on $\frac{1}{2}$ per cent. bile salt agar medium and the colonies identified by fermentation and agglutination reactions. *V. cholerae* produces acid but no gas from glucose, saccharose, mannite and maltose; many strains are late lactose fermenters. When grown in peptone water the organism gives the cholera-red reaction. The test is done by adding pure sulphuric acid to a peptone water culture. Agglutination of the organisms occurs up to a titre of 1 in 1,000 or more with the specific serum, after the tenth day of the disease. It should be noted in this connection that as a rule satisfactory results may not be expected until 5 to 6 days after the onset of the illness, and that positive results have been recorded with sera from carriers or vaccinated persons.

There are many diseases which may be mistaken for cholera and an attempt should always be made to differentiate them. Severe gastro-intestinal disturbance, occurring commonly in summer, may simulate cholera. In infants summer diarrhoea may cause symptoms resembling those of cholera. Acute

bacillary dysentery, algid malaria, arsenic poisoning, meningitis in children and many other conditions in an endemic area have to be distinguished from cholera. The history often helps, a differential blood count and blood examination should also be done, but the final criterion is the detection of *V. cholerae* in the stools.

Prognosis. The mortality rate varies in different epidemics from 30 to 80 per cent., being the highest at the onset. In certain parts of India, the incidence and mortality of cholera exhibit a marked seasonal variation. It is higher in the first and last quarters of the year, and lower in the second and third quarters. Young children, pregnant women, aged and debilitated people, alcoholics and chronic nephritics do badly. A severe and prolonged collapse stage, uræmic symptoms and hyperpyrexia are unfavourable signs, but with modern treatment these can often be avoided.

Unfavourable signs are great cyanosis and restlessness with complete failure of the pulse at the wrist and especially in the brachial artery. The severity of a case can be estimated from the degree of concentration of the blood; the specific gravity of 1066 and over is of grave prognostic significance.

Prophylaxis. Of all the quarantinable diseases cholera is the one in which prophylactic measures are of great influence in prevention of infection. Theoretically, quarantine should be an efficient protection against the introduction of cholera into a community, but unless they are stringent and thoroughly carried out, quarantine regulations are of little use. Quarantine, inadvertently carried out, may sometimes actually increase the risk of an epidemic, by fostering a false sense of security and thus lead to neglect in the observance of domestic, municipal and personal cleanliness and an uncontaminated water and food supply. Moreover, in consequence of the intimate association of a number of individuals in a quarantine station, the number of carriers is likely to be increased. Cholera in the main is a water-borne disease and attempts should be made to ensure a pure water supply. All drinking water and all water in which dishes and other articles used in the preparation and

serving of food are washed, should be boiled. Water can be also made safe by treating it with potassium permanganate or bleaching powder. Disinfection of wells, ponds, etc., should form a part of every public health programme. Pure water should be cheap and within the reach of the poorest classes. Flies play an important part in the spread of the disease. All food should be protected and measures should be adopted to destroy their breeding place.

Experience in the cholera epidemics has shown that great care should be taken to preserve the general health. Fatigue, chill, excess in alcohol or in dietary should be avoided. It must be remembered that the use of purgatives, especially the saline purgatives, may precipitate an attack of cholera in a carrier or those who are liable to attacks of indigestion.

Tomb used extensively a mixture of essential oils which is made up as follows:—Oil of cloves 5 min., oil of cajuput 5 min., oil of juniper 5 min., aromatic sulphuric acid 15 min. and spirit of ether 30 min. Half to one dr. of this mixture is given in 1 oz. of water as a prophylactic measure. Once the disease has developed this mixture is of little or no value and there is some evidence to show that in excessive doses it causes damage to the kidneys and suppression of urine.

Anticholera inoculation. Vaccines are obtained by suspension in normal saline of the growth of 24-hour old agar cultures and killing the vibrios by heat at 56°C. to which 0.5 per cent. phenol is added as a preservative. In order to ensure full immunisation, a sufficient dose should be given. The usual method is to give two injections, consisting altogether of 12,000 million organisms. It is advantageous to use vaccine which is made from local freshly-isolated smooth strains. For a single injection 8,000 million vibrios is the usual dose employed, but the best recommendation that one can make is to employ the strongest dose that can be tolerated without producing an excessive reaction. While vaccination by single injection is of some value, vaccination by two injections should be the method of choice. Statistics show that the total

mortality is twenty-five times as high in the non-vaccinated as in the vaccinated. Vaccination by the mouth has also been practised according to the principle enunciated by Besredka (1927). The vaccine is made from a thick suspension of organisms killed by heat, carbolic acid or alcohol ; each dose consisting of 10-100 thousand millions of vibrios contained in a pill is given every day on an empty stomach and usually 3 to 5 doses are employed. Russell (1927) made comparative tests of anticholera vaccine and the oral bilivaccine, and he showed that the effects of anticholera inoculation is superior to the three doses of bilivaccine. The immunity only lasts for about six months.

Bacteriophage. The value of cholera bacteriophage as a prophylactic against cholera has been investigated by different workers in India and a more thorough trial should be given before its value can be definitely ascertained. d'Herelle and Malone claim that oral administration of bacteriophage is of value in treatment and that its addition to well water helps to cut short epidemics of cholera. Asheshov introduced a mixture of three types A, B and C and he is of opinion that all three must be present to be effective against cholera vibrios. Mixtures of all three have been tried as a prophylactic measure by adding to the water of wells in amounts of 50 c.cm. in the villages and towns in one district in Bihar, with the result that there was a marked drop in the incidence of cholera. Russell however holds a different view. The supporters of bacteriophage explain failure in immunising people against cholera by phage, by bringing forward the theory of lack or absence of a sufficient number of active types of bacteriophage.

Treatment. The disease being a sudden one the patient is usually seen when he is in a distressed or even in a collapsed condition. It is important to realise that as soon as symptoms suggestive of cholera appear, the patient should lose no time in going to a hospital. Medicines given by mouth at this stage are absolutely useless. The patient should be kept in a horizontal position in a warm bed and the foot of the bed raised. Nursing is important ; a careful recording of the temperature including

rectal temperature, pulse, reporting the number and character of the stools, seeing that the patient avoids chills and gets adequate attention, are essential to the proper conduct of a cholera case. On no account should the patient be allowed to get up to pass his stools but be made to use the bed-pan. In very severe and fulminant cases, the incessant use of the bed-pan exhausts the patient's strength and a better plan is to put a waterproof sheet which can be changed every few hours under the patient and to pack the buttocks with tow or cotton wool. It must always be remembered by the attendant that the stools are highly infectious and rubber gloves should be worn when washing the patient or changing bedding. Sips of water, soda water or *dab* (cocoanut) water are given frequently to allay thirst. Cramps may be relieved by friction and massage of the limbs, or if very severe by a small injection of morphia or even by repeated small inhalations of chloroform. Blankets and hot water bottles help to maintain the body temperature. All food should be withheld during the acute stage of the disease, but the intake of fluids encouraged. The course of the disease is so rapid that the successful treatment of patients suffering from cholera entirely depends upon the careful assessment of the varying phases of the disease and the application of rational methods of treatment. In no other disease is a closer collaboration between the nurse and the doctor necessary to bring about a cure. In cholera two main lines of attack are essential to counteract the effect of the powerful toxins of cholera on the body, to eliminate the toxins formed and to destroy the cholera vibrio and prevent the occurrence of uræmia. It is essential that treatment should be begun as soon as possible, the symptoms be watched carefully and the treatment be modified as the case develops so that the collapse stage and other deadly complications may be avoided. The best palliative method as yet devised for the treatment of cholera is that introduced by Sir Leonard Rogers in Calcutta between the years 1906 and 1915 which most rapidly and satisfactorily replaces the fluids, salts and alkalies lost from the body tissues. The only specific treatment of cholera, which aims at the destruction of the

cholera vibrio is the administration of bacteriophage, which by parasitization of the cholera vibrios destroys them or renders them innocuous. It must be definitely understood that bacteriophage can only attack vibrios, it cannot heal the lesions already developed nor counteract the toxins already formed, so that the use of bacteriophage alone without other measures is not rational. The treatment should therefore be directed along the following lines.

Restoration of fluid and prevention of acidosis. The great loss of fluid from the body is the essential factor to be combated and the specific gravity of the blood is the key to estimating that loss and hence the amount of fluid to be replaced. The profound fall in blood pressure, cyanosis, loss of elasticity of the skin and restlessness are largely due to dehydration. Restoration of fluid in itself revives the patient in a marvellous manner. The amount to be injected varies from three to six pints in an adult male, in accordance with the degree of concentration of the blood, as shown by the specific gravity and its effect on the pulse, which should be quite full and of good tension at the end of the infusion. In children of about six, one pint can usually be injected with safety.

Salines. Rogers found that in mild cases of cholera the loss of fluid was on an average 35 per cent. of the total body fluid ; in severe cases requiring saline injections but recovering, it was 52 per cent. ; and in cases ending fatally in spite of saline injections it was no less than 64 per cent., or nearly two-thirds of the total. The loss of fluid can be rapidly estimated by taking the specific gravity of the blood by means of a series of small bottles containing glycerine and water of every second degree from 1050 to 1070. The normal specific gravity of blood is about 1056 to 1058 and a rise to 1063 indicates the loss of three pints of fluid, 1064 of four pints, and 1065 of five pints. This furnishes a simple guide for the amount of saline to be injected. Isotonic salines were first used in the treatment of cholera as early as 1831-32, but the improvement was of short duration, the death rate being about 84 per cent. Later, clinicians tried it with similar results. The

reason of this is that in severe cases of the disease chlorides may be lost from the blood even in greater proportions than the fluid. This leads to a vicious circle and the fluid injected into the vein runs out through the intestinal mucous membrane denuded of its epithelial lining. This led Rogers to introduce the use of stronger or hypertonic salt solution to replace the great loss of salts and to help the retention of the fluid in the blood vessels. It is held that the chlorides combine with the cholera toxin and are excreted through the kidneys. Injection of gum solutions was recommended by Bayliss in cholera, but a colloid solution such as this helps to retain the toxins in the blood and has therefore been given up.

In cholera there is a marked reduction of the alkalinity of the blood which leads to the development of acute nephritis and uræmia. It was shown by Sallard (1910) that no amount of alkali given by the oral route rendered the blood of uræmic cholera patients alkaline but addition of sodium bicarbonate to saline solution reduced the death rate considerably in cases of post-choleraic uræmia. It was shown by Megaw (1911) that once uræmic symptoms had ensued, it was too late to save the patients by alkaline injections. An estimation of the alkalinity of the blood in cases of cholera showed that in no less than 79 per cent. it was reduced from N/45 to N/100, or even less. In severe cases, dying of post-choleraic uræmia, the alkalinity was reduced to N/100 or less, and once that point was reached it was too late to save the patient by intravenous injection of alkaline solutions. Cases presenting a lower degree of reduction may recover under alkaline treatment. These observations, as regards reduction of salts and alkalinity, and the need for hypertonic and alkaline solutions were confirmed by other workers independently.

The *hypertonic saline* consists of sodium chloride 120 gr., calcium chloride 4 gr. and water 1 pint. The *alkaline solution* contains sodium bicarbonate 160 gr., sodium chloride 90 gr., water 1 pint. The bicarbonate may be sterilised in an autoclave, and added to the boiled saline solution.

The following are the chief indications for the use of saline in cholera:—(1) Specific gravity of blood over 1058 ; (2) blood pressure below 70 mm. Hg. ; (3) coldness of the extremities with a feeble pulse at the wrist ; (4) cyanosis, restlessness and cramp.

The intravenous injections of saline should always be controlled by the specific gravity of the blood ; as a guide for the quantity of saline to be injected in each case it may be stated that a specific gravity of 1064 or over requires 3 to 3½ pints of saline ; 1062 to 1064 requires 2 to 3 pints ; 1060 to 1062 requires 1½ to 2 pints ; 1058 to 1060 requires 1 to 1½ pints.

In all cases of collapse, 1 pint of alkaline saline is given intravenously at each injection, together with 2, 3 or more pints of the hypertonic saline in accordance with the concentration of the blood. The early and persistent use of alkalies has practically eliminated death from uræmia in cholera. The temperature of the fluid to be given intravenously should not exceed 80°F. except in very rare cases where the rectal temperature is several degrees below normal when the saline may have to be given at blood heat. In cholera the temperature may be suppressed in the collapse stage but it usually rises above normal during the reactionary stage following collapse and even in cases untreated by saline and may pass into fatal hyperpyrexia, which has to be carefully guarded against after intravenous injection of salines. This may be done by taking the rectal temperature in all cholera cases, and if it is over 100°F. (it may be as high as 108°F. in the collapse stage with cold limbs), the salines should be run in at room temperature in the tropics, with a mean temperature of about 80°F. Antipyretic measures, in the form of hydrotherapy, have to be taken if the temperature rises to 104°F. or over, after intravenous injections of salines. Hyperpyrexia is a grave complication in cases of cholera treated with salines.

The rate of infusion should be carefully controlled and should be about 4 oz. per minute as long as the pulse is not fully restored ; in this way 4 pints can be given in 20 minutes. The cannula should be tied preferably in the median

basilic vein. If the flow is greatly reduced or stopped by strong vasomotor contractions 1 c.cm. of pituitrin can be given. The infusions should be repeated if the specific gravity rises to 1063 or over, and the blood pressure is 80 mm. or less ; cramps, restlessness and cyanosis are clear indications for repeating the intravenous injections of hypertonic salines. If the pulse pressure, as represented by the difference between the systolic and diastolic readings is under 20 mm. the use of further saline is indicated, but an increase of 4 mm. in the pulse pressure is an indication for stopping the infusion. During 1915-19 cases treated in Calcutta with saline, the mortality was 20.8 per cent.

In addition to intravenous saline, Rogers combined hypodermic injections of 1/120 gr. of atropine morning and evening in acute cases of cholera. Rogers' method of treatment has been favourably reported on by all those who have tried it.

Strophanthin 1/250 gr. or pituitrin $\frac{1}{2}$ to 1 c.cm., may be given along with saline and are valuable in sustaining the heart and raising the blood pressure. Adrenalin chloride may be used either alone or along with the saline, but the effect is transitory.

Along with intravenous salines, $\frac{1}{2}$ to 1 pint of the alkaline isotonic saline with glucose should be given per rectum every four hours until 2 pints of urine are passed in 24 hours, and they will often be retained and absorbed with much benefit, especially in milder cases not requiring injection.

Relief of toxæmia. Antiserums. Although on *a priori* reasoning antiserum treatment would be the ideal method of treatment in a condition where there is such marked toxæmia the experiments carried out so far have been inconclusive. No satisfactory antiserum has yet been prepared.

Drugs. Kaolin or aluminium silicate, was first used in the treatment of cholera by Stumpf in 1906. Walker (1921) advised giving half and half suspension of finely pulverised kaolin in water to drink *ad libitum* with the idea that it will absorb the toxins and so lessen their absorption into the circulation. Colic and the tendency to vomit is at once arrested. During the War, dysentery and cholera in the German armies, were treated successfully with kaolin. Kaolin is sometimes combined with charcoal.

The rate of mortality in cholera during an epidemic varies greatly, thus in certain endemic areas in Bengal the mortality varies between 45 and 75 per cent in different seasons of the year. Thus in order to prove the efficacy of any drug it should be given throughout the whole year with alternate cases of control. In this way treatment with opium and morphine combined with mineral acids which was at one time quite prevalent, has been shown by Rogers to be not only useless but positively harmful, the mortality due to uræmia being very high. Opium eaters and smokers do badly when they are attacked with cholera. Rogers suggested treatment with potassium permanganate in form of pills with kaolin powder and vaseline and coated with sandarach varnish or salol with the idea of oxidising toxins. Two-grain pills are given every quarter of an hour for the first few hours, and then every hour till the stools become green and less copious, indicating the presence of oxidised bile. One hundred or more grains have been given without any harm. Rogers also obtained good results by giving permanganates by mouth along with hypertonic salines.

Calomel and camphor in $\frac{1}{2}$ gr. doses with 2 gr. of Bicarbonate of soda can be administered every half an hour till the colour of the evacuation changes to green after which the interval is prolonged with almost the same results.

Many other intestinal antiseptics have been used but with little success, but are still recommended. When given early the disease is said to have been aborted. Tomb (1924) found that the essential oils mixture reduced mortality and was also of prophylactic value. The mixture was given in doses of 1 dr. in $\frac{1}{2}$ oz. of water every half hour until sickness and purging ceased: usually five or six doses were necessary. With this treatment the mortality was reduced to 20.5 per cent., but in collapsed cases the death rate was 72 per cent. against 20 per cent. with hypertonic saline, and 16.6 per cent. with 2 gr. potassium permanganate pills every fifteen minutes (according to Rogers' plan). Essential oils mixture has been found to be irritant to the stomach and produces sudden suppression of urine.

Bacteriophage. See bacteriophage therapy, page 808.

Summary. The position regarding treatment of cholera is that in serious cases the hypertonic and alkaline infusions, combined with permanganate pills and kaolin, or both, orally, has reduced the mortality rate in dangerous forms of cholera to one-third of the former rate. Unfortunately these methods can only be tried in well-equipped hospitals or in the homes of well-to-do people. In villages and other places where only permanganate and kaolin are available, these are the only remedies that can be used; volatile oils may be tried in mild cases. Whenever possible bacteriophage should be given a trial. In preventing infection among the contacts bacteriophage is useful.

Wu Lien-Teh et al (1934) summed up a standard of treatment of cholera in the following lines:—

“(1) *Premonitory diarrhoea.* For this stage bismuth and soda or Tomb's essential oil mixture, or kaolin and calcium permanganate pills may be given. Atropine may be injected. In India, ol. ricini $\frac{1}{4}$ oz. is often prescribed. Opium is not recommended, but 15 min. of it are added to the ol. ricini if the case is not cholera, to be followed by 10 min. of acid hydrochloric dil. in 1 oz. of water every $\frac{1}{4}$ hour for 4 hours.

(2) *Stage of copious evacuation and collapse.* It is at this stage that the patient seeks medical aid, and is therefore most often seen by the doctor.

(a) On admission atropine gr. 1/100 is injected hypodermically.

(b) Take the specific gravity, blood pressure and rectal temperature.

(c) If the blood pressure is not over 70 mm., or the specific gravity is 1063 or more inject intravenously 3 to 6 pints of fluid, according as the specific gravity is 1063-4-5-6. That is to say, if the specific gravity is 1063 inject 3 pints, if 1064 inject 4 pints and so on. In the case of a child or woman the volume of injection is reduced accordingly. The first pint is the alkaline solution, consisting of 90 gr. sodium chloride and 100 gr. sodium bicarb. and the remainder is hypertonic saline solution.

The speed with which the fluid is injected may be fast or slow, namely 4 oz. per minute, i.e., 1 pint in 5 minutes or $\frac{1}{4}$ -1 oz. per minute, i.e., 1 pint in 20 minutes.

If the rectal temperature is normal the temperature of the fluid should be the same. If the former is 100°F. then the latter ought to be 94°F., and if 96°F. then 102°F. In this way the danger of developing hyperpyrexia is avoided.

The infusion must be repeated if the blood pressure falls again to 70 mm. or under, or if the specific gravity of the blood rises to 1063 or

over. Other indications are restlessness, cyanosis, cramps, failing pulse, etc.

The repetition of injection depends on the condition of the patient; some require one pint in 24 hours while others as many as 50 pints. Each time 1 pint of alkaline solution must be injected before the hypertonic.

Calcium permanganate water, 1 to 6 gr. to 1 pint, may be sipped or 2 gr. pills every 15 minutes for the first two hours and every half hour for the rest of the day may be ordered. Kaolin 7 oz. (200 gm.) in 14 oz. (400 c.cm.) may be given in bowlfuls every half hour.

After rallying, the blood pressure will go up to 80 or 100 mm. Normal saline to which glucose is added may be injected *per rectum* at the rate of $\frac{1}{2}$ -1 pint every 2 hours and later every 4 hours until urine is passed freely. For the circulation, 10 min. adrenalin may be injected intravenously together with the saline solution upto 120 min. in 24 hours.

If the urine remains suppressed after 12 to 16 hours and the blood pressure is low, 1 to 3 pints alkaline saline solution may be injected intravenously plus 1 c.cm. pituitrin hypodermically. Fifteen gm. of urea may be given orally with benefit."

FOOD-POISONING

In former years the term food-poisoning was used to include a variety of clinical conditions of diverse ætiology. As a result of the work of Savage and others the term is now restricted to certain acute conditions characterised by gastro-enteritis usually of sudden onset and short duration and attacking a number of persons within a short period of time. Excluding cases in which poison is added to food accidentally or with criminal intent, the vitamin deficiency diseases and the peculiar idiosyncracies of individuals to certain food-stuffs (food sensitization or allergy), three classes of food-poisoning may be distinguished:—(1) That due to poisonous foods, (2) that due to certain chemical poisons, and (3) that due to bacterial infections or toxic bacterial products.

Poisonous foods. In this class may be grouped those substances which are consumed through mistake for wholesome food. Poisonous fungi may be mistaken for edible mushrooms. The tap root of aconite has been substituted for horse radish; children may eat the attractive berries of deadly night shade. Rhubarb leaves are poisonous by reason of their high oxalate content and even nutmeg may produce toxic symptoms. Certain tropical fish give rise to symptoms of acute food

poisoning and apparently sound mussels not infrequently cause illness which has been attributed to a poison, mytilotoxin, apparently generated under unknown conditions. Sprouting potatoes may cause toxic symptoms due probably to the elaboration by the action of micro-organisms of a poison called 'solanin.' The grains of cereals may be attacked by ergot fungus (*Claviceps purpurea*) and cause gangrene of the extremities or nervous lesions. Lathyrism which is caused by a poisonous amine has been described elsewhere.

Chemical poisons. Chemical poisons sometimes find their way into foods accidentally. Epidemics of peripheral neuritis have been caused by the presence of arsenic in beer and also in fruits and vegetables; chronic lead poisoning may arise from the use of soft water. Copper, lead and chromium compounds have been used as agents for colouring food-stuffs. Antimony oxide is used as a cheap substitute for tin oxide in enamelling hardware and outbreaks of poisoning have been caused by partaking of lemonades prepared in jugs of this kind, due to the tartaric acid or citric acid dissolving a considerable amount of antimony. Tinned food may be contaminated by the metal derived from the container, but tin seems to be innocuous; the same probably holds good for aluminium. Various preservatives are added to food-stuffs but they should be either prohibited or their use controlled. Such substances are boric acid, formalin, benzoic and salicylic acids, sulphurous acid and sulphites.

Bacterial Food-poisoning.

The conception of food poisoning has undergone considerable change in recent years. It was formerly believed that food poisoning was due to a series of toxic amines called ptomaines, which appear during the later stage of protein putrefaction, but this theory is now discredited. Ptomaine bodies are relatively non-toxic to laboratory animals except in doses much larger than are likely to be consumed under ordinary conditions. Moreover it has been observed that outbreaks of food-poisoning arise from the consumption of food which is quite normal in naked-eye appearance, while protein putrefaction causes such marked decomposition of the food-stuffs that it is impossible to eat them.

Bacterial food-poisoning is now recognised as a distinct clinical entity with symptoms of acute gastro-enteritis arising as a result of consumption of food infected, in a large number of cases, with an organism of the salmonella group or food containing preformed toxic bacterial products. Our knowledge however is still imperfect and other organisms belonging to different groups as well, or other causes may also be responsible. In infections with these organisms the symptoms appear in from 6 to 24 hours after consumption of the food-stuff but may be delayed for 4 days. The patient becomes ill with severe headache followed by nausea, vomiting, diarrhoea and abdominal pains; some degree of

pyrexia may be present, but as a rule, it is slight and recovery generally follows.

Food-poisoning bacteria. *Salmonella* group. It is not possible at present to demonstrate the cause of every outbreak of food-poisoning, but the organisms of the salmonella group are those most frequently encountered. Morphologically and in general characters these organisms resemble the paratyphoid bacilli. In fact it has been observed that *Bact. paratyphosum* B (not A) may produce symptoms of acute food-poisoning, but this is very rare. They are small non-sporing bacilli, multi-flagellate and actively motile; all of them ferment glucose usually with gas production, but they do not ferment lactose and saccharose, and in this respect are allied to the bacilli of the typhoid and dysentery group. Some twenty or more types have been found which can be differentiated from one another by serological tests. The commonest member of the group responsible for food-poisoning outbreaks is *Bact. enteritidis ærtrycke*; *Bact. enteritidis Gaertner* is considered to be a less common cause of bacterial food-poisoning. Morphologically and culturally the latter resembles *paratyphoid* B and *Bact. ærtrycke*, but can be differentiated by agglutination reactions.

Although the salmonella group of organisms is regarded as an important factor in the causation of food-poisoning, many outbreaks have occurred where no organism belonging to this group could be isolated. Savage (1920) reported that out of 112 outbreaks in the British Isles, bacilli of the salmonella group were isolated in 39 outbreaks, and in subsequent observations the same worker could not find these organisms in the majority of cases. Many reasons have been advanced to explain this failure. It has been stated that certain outbreaks are due not to infections with the living organisms but to ingestion of toxins elaborated by the bacilli in the meat. These toxins are thermostabile and therefore withstand heating. Savage and White (1925) gave agar plate cultures of *Bact. ærtrycke* either alive or killed by heat at 60°C., to young rabbits orally which produced congestion of the stomach with petechial hæmorrhages; similar results were produced by *Bact. enteritidis*. Several workers have found that culture of the organisms of the paratyphoid enteritidis group are toxic to laboratory animals after some day's growth especially after parenteral injection.

The available evidence at present indicates that outbreak of poisoning following consumption of contaminated food is an infection and not an intoxication, because of the fact that poisoning follows consumption of made-up dishes where cooking has been inadequate; moreover the amount of toxin that would be necessary to cause fatal symptoms is considerable when given by the oral route. Jordon (quoted by Topley) is of opinion that in human outbreaks toxins are of little importance, because (1) well-cooked food is less liable to cause poisoning than raw or imperfectly cooked food; (2) outbreaks are generally due to sausages, meat pies, puddings and jellies which are not, as a

rule, sufficiently cooked to destroy all the bacteria; (3) ordinary roasting or boiling often fails to sterilize meat; (4) persons eating properly cooked meat often escape, while those partaking of raw or partially cooked meat are often attacked; (5) the blood serum of the patient often contains agglutinins some days after the attack, which are not likely to be formed against toxic substances alone. The reason why the bacilli cannot be recovered on bacteriological examination in many cases is due to the fact that the original food causing the outbreak is more often not examined for the causative organism. Moreover it may be mentioned that many outbreaks of food poisoning are not of this nature, but are of entirely different ætiology.

Other organisms. Various other micro-organisms besides the bacilli of the salmonella group have also been held responsible for food-poisoning outbreak. *Bact. morgani* has been found in a large number of cases of summer diarrhoea. Dysentery bacilli are occasionally the cause of acute food-poisoning outbreaks, which may sometimes be indistinguishable from outbreaks caused by the salmonella group. Dysentery bacilli of the Sonne type have been incriminated. Evidence at present suggests that it is conveyed by some carrier of the bacilli, and the symptoms begin with vomiting, passage of blood and mucus in the stools. Streptococci have been incriminated, *Bact. cloacæ*, a coliform organism, met with in sewage has caused outbreaks in some places; similarly *Proteus vulgaris*, *Ps. pyocyaneus*, the commonly distributed putrefactive organisms, are said to have been responsible for food-poisoning.

Toxic bacterial products. It has already been stated that the consensus of opinion regarding food-poisoning is that the primary cause is a bacterial infection and not an intoxication. Excluding botulism which forms a distinct clinical entity and is caused by the preformed toxins of *Cl. botulinus*, certain cases of food-poisoning have been attributed to the formation of toxic products in the food by the activity of the micro-organism. In contra-distinction to infection with the organisms of the salmonella group, the symptoms of poisoning arise within a few hours of the ingestion of the food, especially canned foods. In support of the intoxication theory Arnold (1929) stated that puppies kept in a hot room and fed on meat culture in which *Bact. enteritidis* had been growing for 24 hours, and which had subsequently been boiled for one hour, suffered from vomiting and diarrhoea. He is inclined to believe that the toxicity of meat culture is increased by heating as a result of the hydrolysis of the metabolic products in the meat. Though this still lacks confirmation it may serve at present to explain the causation of toxic symptoms after feeding with infected meat which has been cooked before consumption and in which no organism has been found subsequently.

Considerable attention has lately been directed towards a form of food-poisoning caused by the toxins of staphylococcus. A number of outbreaks due to this has been recorded, the symptoms appear in two

to three hours and consist of nausea, salivation, abdominal pain, vomiting, extreme prostration and profuse diarrhoea. *Staphylococcus* forming yellow pigments have been identified in these cases; poisoning symptoms are said to be caused by entero-toxin produced by this organism. Filtrate of *staphylococcus* culture has been found to contain several toxic substances, such as hæmolysin leukocidin; dermatoxin, lethal toxin, and entero-toxin producing food-poisoning symptoms. Ordinary laboratory animals are not affected by the *staphylococcus* toxin; in man also certain conditions are necessary for the production by the *staphylococci* of toxins in sufficient amount to prove harmful. In addition all strains of *staphylococci* do not produce entero-toxin of food poisoning, and that is why *staphylococcus* food-poisoning is not so frequent.

Mode of infection. Meat is perhaps the most common article through which food-poisoning occurs. This is contaminated either in the process of cooking or during storage. In this respect veal, pork and beef are the chief offenders, mutton being less liable to be contaminated. Tinned meat and tinned fish are frequent causes of food-poisoning. They may be contaminated before tinning by improper preservation or insufficient cooking, even if wholesome at the time the tins are opened, they are liable to bacterial contamination later on. Fresh meat is also responsible in some cases; but it is generally found that it has been previously stuffed, recooked or otherwise treated. In some cases the food has been allowed to stand for a time before consumption. Numerous epidemics of food-poisoning have also been due to eating shell fish such as mussels, oysters, lobsters, crabs, etc. Vegetables and fruits may likewise be contaminated, and milk which is a common article of diet, has on several occasions been the cause of an outbreak. It is important to remember that the food generally appears to be quite normal in appearance. The bacilli in the food-stuffs may also be unevenly distributed so that different preparations from the same meat may vary in infectivity. This is a frequent observation with regard to canned foods, and is due to the fact that the original contamination may be localised, or through defective process of sterilisation some cases may fail to be raised to the requisite temperature to kill the bacilli.

The manner in which these food-stuffs are contaminated is not definitely known. An infected animal may be the source or it may be due to the flesh of a healthy animal being contaminated during the process of preparation. It is not known how frequently animals harbour *salmonella* bacilli. *Bact. ærtrycke*, *Bact. enteritidis* and *paratyphoid* bacilli have been recovered from many sick animals. Mayer (1918) found that in 48 food-poisoning outbreaks due to *Bact. enteritidis*, meat was derived in 23 instances from animals known to be ill before slaughter. In 77 outbreaks caused by organisms of the *salmonella* group, 10 were due to food derived from sick animals. On the other

hand, sources of contamination during the course of preparation are many. *Salmonella* bacilli are occasionally present in the intestines of pigs and cattle and the meat may be soiled during slaughter. The possibility of existence of a human carrier should not be lost sight of; Fletcher was able to isolate *Bact. ærtrycke* from the fæces of patients convalescing from dysentery or enteric fever. Rats and mice suffer from infections with *salmonella* bacilli and fly infection has also been suggested. Large gaps at present exist in our knowledge of the mode of infection.

Laboratory diagnosis. The diagnosis of food-poisoning is made primarily from the clinical symptoms. To confirm it a bacteriological examination of the following materials should be done, (in the case of negative bacteriological findings, tests for detection of chemical poisons should be carried out)—(1) actual food consumed, (2) vomit, fæces of patients and blood for agglutination, (3) fæces and blood of suspected carriers, (4) blood, spleen, liver intestine in fatal cases.

Examination of fæces and vomit frequently gives positive results in *salmonella* infection. The contaminated food should be examined for the presence of the bacilli of the *salmonella* group by cultural methods, or it may be suspended in saline and injected into mice; the results are not always reliable. Canned foods are examined on similar lines.

Micro-organisms are not found in the blood stream except in fatal cases. At the earliest possible moment agglutination tests should be done with the patients' sera, and repeated at least twice at intervals of 7 to 10 days in order to detect any rise in titre.

Prophylaxis. The hygienic precautions to prevent food-poisoning primarily concern Public Health workers. A thorough systematic inspection of meat in all slaughter houses is essential. It may be stated briefly that cleanliness in the production and handling of food-stuffs is an efficient safeguard against many of the infections carried by food, particularly the bacterial ones. The diminution of human contact and handling in the preparation of preserved foods, greatly reduce the occurrence of food-poisoning as the pathogenic organisms occasionally gain access to the food through the agency of human beings harbouring the bacilli. In respect of certain diseases conveyed by food such as tuberculosis and helminthic infections from meat, naked eye examination may sometimes be helpful to detect the unhealthy stuff. This is not however useful in cases of bacterial infections of the *salmonella* group where the food-stuffs apparently look normal in appearance unless of course

the food is decomposed. Methods adopted in the prevention of infection may be roughly stated as follows:—

Cooking. Cooking of meat and all other food-stuffs is a considerable safeguard against infection and if adequate, would destroy all infections. It must, however, be remembered that in some cases the temperature in the interior of the meat during the process of cooking may not rise sufficiently high to completely sterilise the food. This is especially true of canned foods which may contain living organisms even after heating to above the boiling point for an hour or more, and several workers have shown that 70 per cent. of canned foods are not sterile.

Pasteurisation. Adequate pasteurisation seems to be a complete protection against infections present in milk. For effective pasteurisation much depends on the adequacy of the process. The temperature preferred is about 143°F. maintained for half an hour, if the temperature falls below that, the process will not be efficient. After pasteurisation or boiling, milk should be rapidly cooled as it has been shown that enormous increase of bacteria occurs during the process of slow cooling in the preparation of ice-cream after preliminary heating.

Refrigeration. The function of the refrigerator is to retard the growth of bacteria and moulds which find their way on to the surface of meat, fish and other food-stuffs. Cold storage undoubtedly tends to diminish the occurrence of food-poisoning, and this is especially the case with such foods as sausages and potted meats. It should, however, be understood that if meat has already been heavily infected refrigeration cannot prevent its rapid decay.

Preserved foods. Canned foods are very often not completely sterilised, in some cases bacterial contamination may occur after the tin is opened and hence it is always advisable to consume the entire content the day it is opened. The formation of toxic products in canned foods depends in some measure on the length of time that has elapsed between preparation and consumption. 'Blown' tins should always be rejected.

Treatment. For curative treatment, measures should be directed towards complete evacuation of the bowel. Rest in

bed is essential. In the early stages, whenever possible, the stomach should be emptied with some emetic or washed out with normal saline solution. A dose of half to an ounce of castor oil to evacuate the bowels is very helpful. No food is generally necessary for the first 24 hours except small quantities of boiled water; later peptonised or citrated milk diluted with an equal quantity of water may be given. The diet should be gradually increased as the symptoms improve. If there is persistent diarrhoea bismuth salicylate with some astringent may be prescribed. Abdominal pain and distension should be treated with turpentine stupes; tincture of opium may be given in form of a mixture. Colonic irrigations with normal saline have also been advocated in cases of persistent diarrhoea. In cases of choleric symptoms and marked collapse, subcutaneous or intravenous injections of normal or hypertonic saline should be given; rectal injection of 1 oz. of glucose in $\frac{1}{2}$ to 1 pint of saline is also of value. Stimulants are frequently indicated in the collapsed stage.

BOTULISM

Botulism is a comparatively rare form of food-poisoning which is due to the toxins elaborated by an anaerobic spore-bearing organism the *Clostridium botulinum*. It is therefore an intoxication and not an infection. The disease was first described by Justinus Kerner in 1820 and the causative organism was isolated and described by Van Ermengen in 1896 from cases which occurred in a certain village in Belgium and where it was confined to those who had partaken of a certain piece of raw ham. During the last few years epidemics of botulism have been reported from America, particularly from California; in Great Britain at the Loch Maree outbreak almost every case proved fatal.

The causative organism *Cl. botulinum* multiplies in the food and produces a toxin before it is consumed, which on ingestion, is absorbed by the gastric mucosa and upper part of the intestine. The fatal dose of the toxin for man has been calculated to be as small as 1/100 mgm. or even less. There are two types of this organism, type A and B; type A produces the most virulent toxin, which affects the nervous system. Three different strains of the organism are known, the Boise (type A),

the Nevin (type B) and the Memphis (type A). Most strains are killed by heat, but the Boise strain can withstand boiling for one hour and hence it is necessary to sterilize food products under super-heated steam. Meyer isolated seventeen different strains from the outbreak of food-poisoning in America. The spores of the organisms of different strains had various resisting power to boiling, some withstanding a temperature of 100°C. for 4 hours while others were killed after boiling for ten minutes or so. A temperature of slightly less than 80°C. destroys the toxin of most of the strains, some toxin however may be so virulent that 0.0001 c.cm. of the filtrate of a culture grown at 35°C. is lethal to a guinea-pig weighing 350 gm. The Boise strains grow most luxuriantly at about the body temperature.

Mode of infection. Nearly all the reported outbreaks were caused by food that had been smoked, pickled or canned and allowed to stand for some time before consumption; it does not follow consumption of fresh food. Investigation into the problem of mode of infection shows that the organism is a normal inhabitant of the surface layer of the soil from where it may gain access to vegetables, fruits, hay, silage and other cultivated products. Occasionally the faeces of animals such as pigs, cattle, horses may contain the bacilli but a healthy human carrier has rarely been encountered.

For botulism to occur the organism must multiply and form toxin in the food before consumption. Though the organism may be present in abundance in soil its occurrence in food-stuffs is uncommon. There are a large number of factors concerned in the survival, germination, and production of toxin by *Cl. botulinum*. The important factors are (1) the presence of spores in large numbers, (2) insufficient heating, (3) anaerobic conditions, (4) too slow cooking, (5) use of food without final cooking. Hence botulism is practically unknown in India.

Botulism differs from the ordinary forms of food-poisoning in that the gastro-intestinal symptoms are absent or insignificant, there is no pain, temperature, pulse and respiration are not affected until near the end. As the symptoms are produced by the toxins, the patient is taken ill within 24 to 72 hours after eating some contaminated food. Onset of dizziness and headache with diplopia are often the first signs of involvement of the nervous system. Later, other nerves are involved with great weakness of the extremities, obstinate constipation, thirst and pharyngeal paralysis.

Diagnosis. The symptoms of botulism are so characteristic that a diagnosis can be made on clinical grounds. The organisms can be isolated from the suspected food or the patients' faeces and vomit. The filtrate of the culture of the organism produces death in mice on intraperitoneal injection.

Treatment. The prognosis is always grave in the disease, and treatment proves effective only in mild cases. The patient

should be in bed and the stomach washed out. Antitoxin has been prepared by injection of rabbits, horses and goats with each type of toxin. Experimentally it has been found that 30,000 neutralizing doses given 24 hours after injection of toxin protects a guinea-pig. In man however the result of antitoxin treatment is not satisfactory. It may be effective only in mild cases. A polyvalent botulinus antitoxin should be given in doses of 50 to 100 c.cm. intramuscularly or in severe cases 50 c.cm. intravenously; 10 c.cm. should be given prophylactically to all those who have partaken of the food. High enema of soap and olive oil has been advocated with the idea that it neutralizes the toxin. Iodine and potassium permanganate have also been used for the same purpose. Certain other substances have been advocated which are said to delay the action of toxin. Morphine is such a drug, and similarly ether anæsthesia has been advocated with the idea that it will delay fixation of toxins by the tissues.

Diseases Conveyed by Food

Besides food-poisoning arising principally from a bacterial infection several diseases are conveyed by food contaminated by bacteria, worms and protozoa. Asiatic cholera though conveyed principally by infected water may also be transmitted by milk, butter and raw vegetables. Enteric fevers are generally conveyed by contamination of water supply, but may also be contracted through the consumption of certain kinds of fish such as oysters, milk, ice cream, butter, cheese, bread and other food-stuffs. Scarlet fever is another disease which may arise from consumption of infected milk and occasionally diphtheria may be contracted in the same manner.

Many other diseases are contracted from an animal source. Tuberculosis of the bovine type in children is generally conveyed by milk and occasionally from tuberculous meat. Undulant fever arises exclusively from goat's milk. Sometimes outbreaks of dysentery and sore throat have been traced to the consumption of contaminated milk. Anthrax is not an uncommon disease among men who handle carcasses of infected animals. Infected meat and foods prepared from meat are common sources of food-poisoning due to salmonella infections, which have been already discussed.

Certain protozoal diseases are said to be transmitted through the agency of food-stuffs; amoebic dysentery may be transmitted by raw vegetables and balantidial dysentery and giardia infections may also arise in the like manner. On the other hand, diseases caused by

worms are transmitted by food alone. Thus *Tænia solium* is derived from eating pork, *Tænia saginata* from eating beef. *Dibothriocephalus latus* may arise from the consumption of certain fresh water fish and the hydatid disease in man is caused by food or water containing the eggs of *Tænia echinococcus*.

A question of great importance in this connection is the source of infection of the food-stuff. It is generally admitted that man alone suffers from cholera, enteric fevers, bacillary dysentery and in these cases infection arises from faecal contamination of the food-stuffs. The infection may either be direct or indirect through contamination of the water supply by an acute or healthy carrier. In tuberculosis, undulant fevers, sore throat, the contamination of milk or meat arises from an animal source. In scarlet fever and diphtheria infection almost always arises from a human carrier.

SPRUE

Sprue also known as diarrhoea alba is a condition frequently met with in the tropics. It occurs in the European and Anglo-Indian residents of India but rarely among the Indians. The disease occurs in Indo-China and in the Southern United States. It occurs chiefly in the debilitated individuals who have resided for long periods in humid tropical climates.

In India it often follows attacks of hill diarrhoea in which watery stools are passed in the early morning. Hill diarrhoea occurs in many hill stations in the Himalayas during the rainy season and resembles sprue in many respects. In both of these conditions physiological derangement of the digestive functions occurs.

A knowledge about the views held regarding the nature of the disease will be useful from the point of view of the rationale of treatment of sprue. In spite of the considerable amount of work which has been done there is no agreement regarding the causation of this disease. There are two schools of thought regarding the causation of the disease.

Certain workers attribute the disease to some diet deficiencies including calcium metabolism. The total and diffusable calcium in the blood has been shown to be considerably lower in sprue than in healthy individuals. Scott formulated the hypothesis that sprue is due to deficiency of calcium metabolism. He noted the resemblance between some of the symptoms of sprue and those diseases in which calcium deficiency is a prominent feature. Vine is of opinion that calcium occurs in the blood in two states, the combined and the ionic form and it is the latter which accounts for the characteristic symptoms of sprue. As a support of this hypothesis it has been shown that the amount of free calcium rises from 6 to 10 mgm. per 100 c.cm. of serum after administration of calcium lactate over a long period. Some believe that sprue

is a deficiency disease caused by the absence of certain vitamins in the diet. MacCarrison was able to produce a sprue-like condition in monkeys fed upon a vitamin free diet. Elder (1925) thought that deficiency in the aminoacids of meat, in addition to fat soluble vitamin A and also vitamin B occurring as result of unbalanced diet in the tropics was the main factor.

Others think that the disease is of an infective nature, and is produced by yeast fungi, streptococci and some other unknown organisms. *Monilla psilosls* a specific yeast has been incriminated. Ashford (1924) produced a rapidly fatal septicæmia in guinea-pigs and white rats by intraperitoneal injections of this organism. Rogers (1918) believe streptococci to be an important factor in the pathogenicity of sprue. They could always be grown from ulcers in the tongue and vaccines from them produce reactions. Manson-Bahr is inclined to believe that there is considerable amount of evidence to show that sprue and amoebic dysentery are closely associated. In some cases the two diseases may exist together or sprue may develop secondarily in a case of amoebic dysentery the former being merely a syndrome of a primary amœbic ulceration of the intestine.

The modern conception of the disease is that sprue is essentially a disorder of the gastrointestinal tract characterised by deficient gastric secretion, of both hydrochloric acid and bone-marrow-stimulating substance, as well as mal-absorption of fats, glucose and calcium. The cause of the gastrointestinal derangement is still unknown, though it has been suggested that it may be due, either to some defective internal secretion or some as yet unknown infective agency.

Treatment. In the treatment of sprue utmost care lies in procuring bodily rest and selecting a very careful dietary for the patient. It is to be understood that sprue is a disease in which the gastro-intestinal tract bears the greatest brunt of attack. Hence if the treatment of the case is begun early in the disease by careful regulation of the diet, very successful results are obtained, while if it is undertaken too late in the period when the absorbing surface of the intestine is damaged the results are discouraging. The treatment must be thorough and persistent. In the advent of the slightest sign of relapse absolute care should be taken, extra food must be discontinued immediately and the patient should be placed on absolute rest and strict milk diet. It should be remembered that most of the patients recover under prolonged and careful dieting and rest in bed. Some cases may run a variable course and prove rapidly fatal. In the chronic cases the treatment has to be

prolonged for several years, there being temporary improvement after relapses.

Dietetic treatment. Rest in bed combined with a purely milk diet gradually increased from three to six pints daily is the backbone of successful treatment in many cases. Some authorities give bananas with the milk but exclude starches and sugars. Others prefer skimmed milk or butter-milk. Fruits such as lemons, oranges, pomegranates, bananas, pineapple, mangoes, etc., are gradually allowed after a week or two. The milk diet should be continued for several weeks till the stools are solid and the patient gains steadily in weight, after some loss for the first week or two. Then eggs, and rusks are given, carbohydrates being increased very gradually. Later, fish and chicken may be given. If the patient is averse to taking pure milk add Benger's food to it. Some clinicians give meat diet alone. For this purpose meat free from fat is minced and gradually increased till one pound is taken daily. Abundant drinks of warm water should be given in between the meals.

It is now being widely recognised that sprue is a disease of the gastro-intestinal tract. Rest to the alimentary canal is therefore the primary idea of dietetic treatment of the disease. As this is the ideal to be aimed at, minimal amounts of food should be given so that the intestine can deal with it. Fat is therefore restricted in the diet, if this is not done additional strain falls on the already overtaxed alimentary canal. Dietetic indiscretion especially an excess of carbohydrates may cause acute enteritis, because the starchy foodstuff undergoes abnormal fermentation with the production of organic acids and gas and consequent abdominal distension. Under these circumstances rational therapy lies in giving proteins as the principal constituent of diet, beginning with one of low caloric value and gradually increasing the quantity. Fairley (1930) thought that this can be attained by giving high protein diet with low fat and carbohydrates. In place of high meat protein, he advises high protein milk powder with a ratio of protein 1.0, fat 0.3 and carbohydrate 1.3. Later (1932) he advocated the use of a dried high protein milk powder (Sprulac) with ratios

of protein: fat: carbohydrate=1: 0.3: 1.3. The scheme of dietary is to give this powder in gradually increasing doses along with full doses of liver (*i.e.* equivalent to $1\frac{1}{2}$ lb. of fresh liver daily) whenever anaemia is present and suitable dietetic modifications. The first diet consists of 1 oz. of sprulac made up to 8 oz. with water every $2\frac{1}{2}$ hours for six feeds; the second one of $1\frac{1}{2}$ oz. made up to 12 oz. every $2\frac{1}{2}$ hours for six feeds; the third, fourth and fifth one of 2 oz. of sprulac made up to 16 oz. with water every two hours for six feeds.

Liver therapy. In addition to the usual dietary treatment, the routine use of liver extract has been much advocated. Various workers have used the whole liver in cases of sprue and have published accounts of clinical cures with the treatment. It has also been suggested that sprue is a disease, due, in some instances to a deficiency of some fraction of the water-soluble vitamin complex, and this is supplied by liver therapy. Though the exact part played by liver in the cure of sprue is not yet settled, its effectiveness is however well known. In order to get the maximum effect liver should be given in as large amounts as required, and by such a route as to ensure maximum utilization. Massive doses of liver preparation when given intramuscularly or intravenously give the best results. Cases that are resistant to oral therapy sometimes show dramatic and complete remissions after parenteral administration. It thus appears that a well-defined threshold requirement for liver preparations exists in certain cases, and to obtain the maximum effect this threshold requirement must be increased. Various preparations have been used, but it is advisable to use a simple unconcentrated product, because certain loss of activity results from too great refinement and concentration which explains the failures met with in these cases.

Liver soup. Liver soup made from fresh calf's liver has earned a considerable reputation. Manson-Bahr advocates its use along with dietetic measures. It may be prepared by adding half a pound of fresh liver in a pint of boiling water and then straining, 10 to 15 oz. may be given in 24 hours and this is regarded as being more easily tolerated than any other form of dietary.

Liver extract. Other liver preparations have also been used, a powdered extract is given in doses of two tubes daily, each tube being equivalent to $\frac{1}{4}$ lb. of fresh liver. Where speed is essential or where liver by the mouth is not desirable hepatex may be tried. It is given in doses of 5 c. cm. per day injected intramuscularly or intravenously for about two weeks or according to the condition of the patient; a total of 30 to 50 c. cm. brings about improvement.

The usefulness of liver therapy is more apparent because of the existence of anaemia. Minot and Murphy (1927) showed that liver was useful in pernicious anaemia as well as in sprue. In the chronic cases the blood picture in sprue resembles that occurring in pernicious anaemia with high haemoglobin index, anisocytosis and the presence of normoblasts and megaloblasts. Castle and his associates showed that in pernicious anaemia some derangement of function occurs which points to deficiency of the haemopoietic function of bone marrow. In the later stages of sprue such changes have been observed; the bone marrow may show hyperplasia or actual aplasia indicating deficient blood production. Though the definite relation between sprue and pernicious anaemia has not been established, the effect of liver therapy in both cases gives some clue to the aetiological factors of the disease.

In addition to the dietary measures 5 to 10 gr. of pancreatic extract or large doses of pancreatin and calcium carbonate or lactate three times a day sometimes produces rapid improvement. Pancreatin in 10 gr. doses after each meal with fifteen min. of 0.2 per cent. of hydrochloric acid before food is the method adopted in some places.

Drug treatment. Drugs should be given with great caution as they are liable to do more harm than good. Bismuth salicylate in 20 gr. doses about two hours after meals checks intestinal fermentation and looseness of the bowels. When diarrhoea occurs 10 gr. of Dover's powder is useful. Parathyroid $\frac{1}{10}$ gr. and calcium lactate 15 gr. thrice daily were recommended by Scott (1932). These are continued for 5 to 6 weeks, the patient is kept on milk diet for three weeks and later given pudding, eggs, fish, carrots and bananas. The calcium and parathyroid treatment if it is to be successful should be started in the acute stage of the disease and persisted in for several months during convalescence. It was at one time considered to have a distinct influence on the course and symptoms of the illness but it is doubtful whether the effects are at all lasting.

Treatment with Batavia powder earned a reputation at one time. This is chemically a carbonate of lime, believed to be powdered cuttle-fish bone or crab's eyes. It has been found to be of great value in elderly people when the diarrhoea persists in spite of all rigid dieting; doses recommended are 15 gr. in cachets, three times daily. For treatment of anaemia, besides intensive liver therapy injections of iron and arsenic may also be found useful.

Vaccines. There are many authorities who are inclined to believe that the disease is of an infective nature and is produced by yeast fungi, streptococci and some other unknown organisms. *Monilia psilosis*, a specific organism has been thought to be the cause of the infection, as it was found in the tongue and in the mucous lining of the intestine. On the results of these findings cases of sprue have been treated with vaccines made from this organism. The injections are given at weekly intervals and five or six such injections are necessary. Rogers believed streptococci to be the important factor in the pathogenicity of sprue and he obtained good results with streptococcal vaccines and his results were confirmed by Nicholls. Small doses such as 0.5 to 1 c.cm. containing 25 to 50 million organisms should be commenced and given once or twice a week.

HILL DIARRHOEA

Hill diarrhoea is a form of flatulent dyspepsia with passage of frothy stools. This condition, as has already been stated, is in many respects indistinguishable from sprue. Hill diarrhoea occurs very frequently in India, especially among the European population frequenting the hills.

With regard to the exact nature of the disease little is known. It seems probable that hill diarrhoea is more than an intestinal catarrh. It was at one time supposed that the food and water supply was responsible for the occurrence of the disease, but the theory of mica contaminated water as the causative agent can no longer be substantiated. It has been definitely proved that in an epidemic area no trace of mica or other solid particles can be found on centrifuging the water collected during the rainy season when the incidence of the disease is at its height.

Many authorities do not consider it to be a separate disease from sprue; hill diarrhoea being only an earlier manifestation of the latter condition. It has been found that the stools of the patients in nearly all cases contain excess of fatty acids, soap and undigested food particles. They are pale, frothy and devoid of biliary colouring matter. Occasionally cases are met with where the symptoms persist and develop ultimately the clinical picture of sprue.

The influence of climate in precipitating an attack of diarrhoea in the hills in an epidemic form, has been recognised. In India it has been shown that a sudden change of temperature is very liable to bring on an attack of this nature in the hills. It has therefore been held that the disease is due to sudden changes in the physical environment encountered before the individual has time to become acclimatised to the conditions prevailing. In the Philippines it was observed that a sudden drop in temperature within a short time after the heat of summer for about 2 months, brought on the condition in an epidemic form. There is no doubt about the fact that in such peculiar and trying condition physiological derangement of the digestive function occurs. This view receives strong support from the fact that immediate cessation of symptoms occurs if the patient is removed to the plains from the hills. Certain predisposing factors, such as, a constitutional weakness of the digestive function, lowered resistance due to long residence in the tropics, rapid changes in temperature in a moist atmosphere with low barometric pressure also play some part in precipitating an attack.

In addition to the prevalent views regarding the ætiology, the question of infection by a specific organism should not be lost sight of. Acton (unpublished) while carrying on investigations on sprue, treated many cases of hill diarrhoea. On bacteriological examination of the stool he could isolate organisms of the dysentery group in many cases. Vaccine therapy with regulation of diet apparently improved their condition. Recently, the subject has been studied in the School of Tropical Medicine, Calcutta. In the majority of cases dysentery organisms, mostly of the Flexner type, were found on examination of stools; a few cases were due to infection with *E. histolytica*. Though these infections may be present in the plains, the peculiar habits of the people in the hills together with other local conditions, are responsible for the development of the condition.

Treatment. The general line of treatment of hill diarrhoea follows that of sprue. Rest in bed with strict milk diet should be the main principle of treatment. Among the drugs recommended are drachm doses of solution of mercuric chloride in water, fifteen minutes after food. Pepsin and pancreatin may also be given after food to help digestion. Many cases have improved from a course of vaccine; prepared from the organisms isolated

from the stool. The cases which are resistant to treatment should return to the plains.

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CHAPTER IV

OTHER BACTERIAL DISEASES

CEREBROSPINAL FEVER

This is an acute specific fever, of world-wide distribution, caused by *Neisseria meningitidis*, occurring both in epidemic and sporadic forms and is characterised by a low morbidity and high case mortality. Infection is spread by 'droplets' from man to man, manifesting itself by septicæmia and an acute form of meningitis involving almost the whole of the cerebro-spinal axis. The disease is most commonly met with in young children up to the fifteenth year and is uncommon over thirty-five years of age. The highest incidence and mortality have been recorded among infants under one year of age. Certain factors favour the spread of the disease and these are climatic influences (particularly winter and spring), fatigue, dirty habits and occupations, over-crowding, bad ventilation and other factors which lower the body resistance. All these predisposing factors are prevalent among the people inhabiting tropical climates.

The causative organism. The Gram-negative intracellular diplococci now known as *N. meningitidis* were isolated by Weichselbaum in 1887 from the cerebrospinal fluid of patients suffering from cerebrospinal fever. This organism is an extremely delicate one and requires special media and special care to keep it alive outside the body. It produces a powerful endotoxin. Formerly the meningococci were divided into four types but some of the recent workers recognise two main groups with subsidiary sub-groups. The exact determination of the type of meningococci prevalent in an epidemic has a most important bearing on the therapeutic use of anti-meningococcal serum. It has been shown that a serum prepared against one group of meningococci is valueless against infection with meningococci belonging to another group. Evidence on this point has accumulated during recent years. Thus a serum prepared with strains prevalent in one country has failed entirely in the treatment of the disease in another country. This is an important factor in the production of an effective therapeutic serum and it is highly desirable that serum prepared from local strains should be employed. The one great practical difficulty in the latter procedure is that it takes a

relatively long period extending to nearly a year to produce a potent antiserum and all that is possible in the face of an epidemic is to use a serum prepared from the known prevalent strains of meningococci.

Mode of infection. The meningococcus gains access to the nasopharynx when it may occasionally set up a rhinopharyngitis. From here it spreads to the meninges. There are two main theories as to the route by which the meningococcus reaches the meninges ; the first is the hæmatogenous route, and the second by a process of direct transmission from the nose to the meninges. Without entering into discussion of the evidence in favour of the two routes, we may summarise the modern and generally accepted view as to the route of infection. The meningococci reach the upper nasal passages through air infection and set up a rhinopharyngitis which in the majority of cases lasts for a few hours or a few days and clears up completely. In a few instances the meningococci may reach the meninges. Recent evidence favours the hæmatogenous route of infection because of the fact that in some cases lesions in other parts such as, endocarditis, renal abscesses, lesions in the joints, etc., occur, but usually late in the disease. These are generally held to be secondary to meningitis though they rank with it as metastasis. It seems probable that transmission of the infection may occur directly or via the blood stream. In support of the latter route of infection it may be stated that in some 25 per cent. of cases the organism can be recovered from the blood in early stages of the disease.

Prophylaxis. The disease is endemic in most of the large cities ; few sporadic cases of post-basic meningitis occur at intervals. The normal carrier rate of meningococcus has been estimated to be as high as 2 to 4 per cent. of the population of some of the large European towns. The carrier rate of meningococci has not been determined for the cities in India, but such investigation is urgently required and will prove of great interest and value. In urban areas there are usually no carriers and the disease is not endemic. For reasons that are not at present definitely established the disease breaks out periodically in epidemic form. The evidence that has been recorded so far shows that a remarkable change occurs in the carrier rate of the general population in the event of an epidemic. From the normal rate of about 2 per cent. the number of carriers increases reaching a figure of about 20 per cent. at the onset of the epidemic and 80 to 90 per cent. during the height of an epidemic. From these figures one is led irresistably to the conclusion that the majority of those developing the disease have not acquired the infection from previous cases but from contact with so-

called healthy carriers. The carrier is in fact the commonest cause of the spread of the disease. The term 'carrier' includes persons with an infected nasopharynx, either one who has not developed meningitis or one who having recovered from the disease itself harbours the organism in his nasopharynx; the former is sometimes called the primary carrier and the latter referred to as the secondary carrier. The great majority of carriers remain infective for about two months, some 15 per cent. of them may continue to harbour the organism for about six months and a small proportion of 2 to 4 per cent. may carry the organisms for as long as a year. Every carrier is potentially infectious and a source of danger.

In the prophylaxis of infection with meningococcus when the main source of contagion is by 'droplet infection' sprayed from a carrier, the essential step in preventing an outbreak or limiting its extension is to reduce overcrowding to ensure adequate ventilation and to encourage the people to lead an open air life. In outbreaks limited to institutions such as schools, etc., a search for the carriers should be made and they should be isolated; but the detection and isolation of carriers in a large community is neither practicable nor possible.

Various methods of local treatment consisting of local application of antimeningococcus serum, antiseptic gargles and nasal douches have been advised from time to time, but when tested with bacteriological control all have proved valueless. They however have a great value both in the education of the public and the removal of gross lesions. For routine use the following is recommended.

Iodine increases the flow of saliva which is inhibitory to the growth of the organisms and acts as an antiseptic and disinfectant drug before and after absorption into the system. This is taken advantage of in the prophylactic treatment. Equal parts of tincture of iodine and honey are mixed and 2 or 3 drops of this mixture are put on the tongue of the isolated carriers several times a day.

Treatment. General management. The patient should be isolated in a well ventilated room until recovery and until the swab from the nasopharynx shows no meningococci. The skin

is sponged with tepid water twice a day. The bowels are kept open by an initial purgative and then by enemata. The bladder should always be watched to see if there is retention of urine and if so a catheter should be used. The position of the patient is frequently changed to avoid hypostatic congestion of the lungs.

Diet. A diet consisting of milk, peptonised or citrated if necessary (2 gr. of sodium citrate in 1 oz. of milk), cocoa, etc., should be given in the early stages; later bread and milk, and as the patient approaches recovery, a liberal diet consisting of fish, chicken, etc., may be allowed. Administration of fluids in all forms—as plain water, glucose or alkaline water (consisting of glucose 2 oz., sodium bicarbonate 4 dr., water one pint), should be freely encouraged from the very onset of the disease, to combat toxæmia. If the patient is unconscious, nasal feeding with citrated milk, small feeds but at frequent intervals (3 oz. every two hours), should be given. If vomiting is present, lime whey, albumin water or peptonised milk may be given and these are often retained by the patient.

Local treatment. Along with general and systemic treatment, local treatment of the nasopharynx should be carried out as reinfection by organisms from these foci may lead to relapses. Such measures as spraying, douching and gargling with antiseptic lotions should be adopted. Spraying with permanganate solution (1 in 1,000), steam spray with zinc sulphate (1 to 2 per cent. solution) or 1 per cent. chloramine solution directly applied to such regions are beneficial.

Specific therapy. The main reliance in the treatment of cerebro-spinal fever is now placed on anti-meningococcus serum together with repeated withdrawal of the cerebro-spinal fluid.

Lumbar puncture. Before the introduction of anti-meningococcus serum the practice of repeated lumbar punctures was considered to be the best method of treatment. This procedure, if performed early and regularly, relieves pressure in the subarachnoid space and thereby lessens the injurious effects on the nerve centres, particularly those in the medulla. In the initial stage the fluid may be under considerable pressure. Characteristic changes in the cerebro-spinal fluid may be noticed on withdrawing it, which are of great significance. In some

cases the fluid may be straw-coloured and coagulate into a solid mass, due to escape of blood plasma into the cerebro-spinal fluid; yellow colouration of the fluid may be the result of admixture with pus. The cellular content of the fluid gives an indication of the progress of the case towards recovery. The cell count may vary between 700 to 30,000 per c.mm. with a predominant polymorphonuclear leucocytosis. Globulin is always in excess. The chloride content, which is normally about 0.73 per cent., is not altered. Stained specimens of the centrifuged deposit should be examined in every case. The presence of meningococci can be demonstrated in a large percentage of cases. It has been found that during the early part of an epidemic of cerebro-spinal fever, diplococci are found to be scanty and extra-cellular forms may predominate. Cerebro-spinal fluid may be withdrawn under local anaesthesia though general anaesthesia may be necessary in some cases. Ker (1929) advised performing successive lumbar punctures with the patient lying alternately on the right side and on the left side, thus facilitating drainage from the ventricle which is uppermost. This is especially important when the fluid from a patient does not show any pus.

Cisterna puncture. Cisterna puncture is of considerable importance in diagnosis and treatment. It is indicated in cases where adhesions in the spinal theca have prevented the withdrawal of fluid by lumbar puncture.

Recently, irrigation of the spinal canal with normal saline at body temperature has been advocated in order to remove the pus and the meningococci and help in the circulation of the anti-meningococcic serum inside the spinal theca. About 30 to 40 c.cm. of the cerebro-spinal fluid is withdrawn by lumbar puncture, and an equal quantity of normal saline at about 100°F. is introduced into the spinal canal. The fluid is redrawn and the process is repeated till the fluid which comes out is clear. As much as 200 c.cm. of the normal saline is used in such a procedure.

Antimeningococcal serum. Jochmann (1906) was the first to introduce antimeningococcus serum in the treatment of cerebrospinal fever and prepared it by injecting horses first with dead and then with living cultures. In the treatment of human cases he gave it in doses of 20 c.cm. subcutaneously or intrathecally. It is however to Flexner (1907) that we owe our present knowledge of serum treatment of cerebrospinal meningitis. He prepared the serum by subcutaneous injection into horses at weekly intervals, of living organisms and autolysates alternately. This serum was standardised by titrating it according to the complement fixation test, and against the autolysate.

in guinea-pigs. From the time of Flexner until now many methods have been developed in the mode of preparation of an antimeningococcal serum so as to obtain the maximum therapeutic effect. A more rapid procedure than that adopted by Flexner has yielded a polyvalent serum of high titre. Numerous strains of different types are included in the preparation. Griffith prepared a monovalent serum using strains of only one type for each horse. It is however important to remember that in the preparation of an immune serum those strains of organisms should be used which are prevalent during an epidemic. Favourable results are also reported from the use of an antimeningococcal serum in which the antibodies have been concentrated by precipitation and dialysis.

The serum is said to produce its beneficial effects by neutralizing the toxin and by directly acting on the organisms, the multiplication of which is inhibited and the organisms rendered more susceptible to phagocytosis. It should be administered by the intrathecal, intravenous and intramuscular routes. Intrathecal and intravenous routes are the usual methods adopted in the acute stage. Before introducing the serum intrathecally, it is most essential that repeated lumbar punctures and efficient saline irrigation of the spinal cord be performed to remove the pus, organisms, etc., which will prepare a field for the reception of the curative serum. The general rule regarding the quantity of the cerebro-spinal fluid to be withdrawn from the spinal canal is that the amount of serum introduced should be half the volume of the fluid withdrawn. On an average, about 40 to 60 c.cm. of the cerebro-spinal fluid is withdrawn by a lumbar puncture and the spinal canal is repeatedly irrigated with normal sterile salt solution at 37°C., till the fluid returns clear. The serum, warmed to body heat, is then injected slowly, the dosage being on an average 30 c.cm. The foot-end of the bed is kept raised for at least two hours after the administration of serum, to facilitate gravitation of the serum towards the brain.

As the disease is essentially septicæmic in nature in the acute stage, about 10 c.cm. of the serum is also given intravenously along with the intrathecal administration for the first

few days to combat toxæmia. If the cerebro-spinal fluid shows abnormal naked-eye features, and the pressure is considerably increased, a much larger quantity of serum may be given intravenously. The whole procedure is generally repeated within eight hours in acute fulminating cases, then given twice daily till the fourth or the fifth day and once daily for the next five days. The intravenous administration of the serum is repeated only during the septicæmic stage and is discontinued when symptoms abate.

The amount of serum to be given to infants should be carefully considered. In children under five years of age, it is inadvisable to give more than 10 c.cm. at a time. In very young children more than a single intravenous injection is not possible and further doses of serum should be given by the intramuscular route.

The results of serum treatment depend upon three factors, namely, (1) the mode of preparation, (2) the method of titration, and (3) the amount injected. The general agreement with regard to the efficacy of antimeningococcal serum is that with a good monovalent serum (especially type 1) the mortality is considerably reduced, the relapses are less and the complications are fewer in number. The earlier it is administered the better is the result and the combined intrathecal and intravenous methods give a lower rate of mortality than the intrathecal method alone. The great drawback of serum therapy is that it is sometimes impossible to obtain a potent antiserum, this is due to the fact that sera used for some time after the start of an epidemic have been prepared from strains which differ considerably from those actually prevalent during the epidemic. If the proper type of sera is available success is marked. Nevertheless, serum treatment is a very efficacious remedy for what is otherwise a very deadly disease, and to withhold serum in any case is inadvisable.

Vaccines. In some cases even in spite of intensive treatment with lumbar puncture and anti-meningococcal serum, the results may be disappointing. Lewkowicz (1924) mentioned the use of meningococcal vaccine in the treatment of this disease but said that the antibodies did not appear in sufficient

quantity in the ventricular fluid to be of real use. Egerton (1932) considers that vaccines are useful in the acute stage of illness. Gayid (1933) is of opinion that usefulness of vaccine is more apparent in the sub-acute and chronic cases. From an observation of more than 200 cases he considers that meningococcal vaccine should have its place in the treatment of cerebrospinal fever. It is indicated in sub-acute and chronic cases, in inflammatory complications, *e.g.*, arthritis and pleurisy, and in cases which are not influenced by the usual treatment. In the acute cases it may be tried when the disease becomes worse in spite of ordinary treatment. It should be realised that in the fulminating and hyperacute cases the vaccine has no effect in the first stage of the illness, and the best method of treating these cases is undoubtedly repeated lumbar punctures and administration of serum intrathecally and intravenously with glucose solution.

The vaccine should be injected hypodermically; the dose for adults in acute cases is 5 millions, in sub-acute cases 10 millions, and in chronic cases 20 millions. The injections are to be repeated every third day, simultaneously doubling the dose. When the amount reaches 600 millions it is advisable to repeat this amount every five to seven days until recovery rather than to increase the dose any more. Six to twelve injections generally constitute a course.

Medicinal treatment. No specific drugs are known to cure the disease and they are only used to relieve symptoms. As in other acute diseases, constipation often troubles the patient and to combat it calomel followed by a saline purge the following morning is a very useful procedure. In very obstinate cases it is necessary to give an enema. For the relief of headache an ice bag should be applied. Antipyretic drugs such as phenacetin with caffeine citrate may be given and repeated if necessary. Counter-irritants in the form of liquor iodii or liquor epispasticus, when applied over the cervical spine, often relieve headache. Hydrotherapy in the form of a tub-bath at 98° F, may also be tried. Vomiting often sets in during the acute stage and interferes with the nutrition of the patient. To allay it a combination of morphine with hydrocyanic acid may be

beneficial, but repeated lumbar puncture is the most efficient measure to prevent vomiting. Sometimes, in intractable cases it is advisable to omit all feeds and keep the patient on glucose and saline injections for 24 to 48 hours. Adequate rest is most essential in the acute stage of the disease and this can only be secured by promoting sleep. In this respect morphine (gr. $\frac{1}{4}$) has been found to be very useful, especially in cases where it is accompanied by delirium and restlessness. But in uncomplicated cases, sulphonal may be tried. Paraldehyde is not effective, as it can seldom quieten a delirious patient in the acute stage; hyoscine should be avoided. Bromides in combination with chloral hydrate have also been used with encouraging results. For cardiac failure digitalin (gr. 1/100) hypodermically should be administered but not strychnine, as this may precipitate convulsions.

Besides the treatment of emergency conditions in the disease, adrenalin plays an important rôle in the treatment of cerebrospinal fever especially in the fulminating types. The secretion of the active adrenal cells is said to be interfered with in this disease and the sudden withdrawal from the circulation of this important hormone may lead to loss of tone of the muscle fibres of the blood vessels and failure of the peripheral circulation. Such a condition is best avoided by treating all cases from the beginning with injections of adrenalin along with general treatment.

Various other drugs have also been tried in the treatment of the disease. Temperature is said to have been brought down by intravenous injections of tartar emetic (1.5 c.cm. of a 2 per cent. solution) in many cases. Salvarsan, neosalvarsan, intramine, hexamine, helmitol, acriflavine or trypaflavine (1 per cent. solution) have been tried both by the intravenous and intrathecal routes but without any definite therapeutic benefit.

Complications may set in during the active stage or the convalescing period of the disease. If cardiac failure with great fall in blood pressure is apprehended, saline infusion at body temperature should be at once resorted to, with other cardiac tonics, namely, injections of digitalin (gr. 1/100), camphor in ether (1 c.cm.) or cardiazol (1 c.cm.), etc. Irritation due to an

intense urticarial rash may be relieved by bathing in a warm alkaline solution or by the local application of one per cent. menthol solution.

For synovitis and the severe form of œdema, pituitrin ($\frac{1}{2}$ to 1 c.cm.) may be injected hypodermically and repeated if necessary. Pneumonia if it develops is treated on usual lines. Joint affections are treated by rest, simple immobilisation of the part, warm applications, etc. If the joint is markedly distended, preliminary aseptic aspiration and later injection of the specific serum (5 to 10 c.cm.) into the joint have been advocated.

For pyelitis and cystitis intravenous injections of hexamine (2.5 c.cm. of a 40 per cent. solution) and lavage of the bladder with two per cent. sodium bicarbonate solution or by simple sterile normal saline often prove useful. Autogenous vaccine, after culture of a catheter specimen of urine, has also been tried with encouraging results. Both flaccid and spastic paralysis have been met with in convalescing cases and these are treated by massage, passive movements and electricity.

PLAGUE

Plague is an acute, specific, infectious disease of short duration with a high mortality. It is one of the greatest scourges of the human race. The disease is caused by *Past. pestis* and is primarily epizootic among rats, ground-squirrels, marmots, etc. At the present time plague is unevenly distributed throughout the world and is endemic in countries such as India and South Africa. The maintenance of infection in these areas depends on the infection of the rodents. Periodically epidemics of plague break out among these animals and man is infected from them as a rule through the agency of the fleas. In this way small isolated groups of cases occur every year. If the endemic foci remain secluded plague is confined to that area but when communication is set up with the surrounding country, the disease assumes an epidemic character. Infection does not occur by direct

contact with the sick, it spreads from place to place thus establishing various foci of plague infected areas. In some cases the disease may be confined to particular buildings, such as warehouses, grain stores, etc. The rats and rat fleas may be carried from one place to another by means of railways, ships or other modes of communication and in this way a secondary focus of plague develops from the primary site of the disease which may serve in its turn as the centre from which infection may spread to the surrounding localities. Plague is always confined to dirty and insanitary quarters and attacks mostly the lowest class of people living under unhygienic conditions. Extreme heat and dryness of the atmosphere are unfavourable for its spread. In India it occurs when the mean temperature is between 50°F. and 85°F. with a high relative humidity.

Bubonic plague. The terms bubonic plague, septicæmic plague and primary and secondary pneumonic plague are in common use but these nomenclatures do not seem to be satisfactory. It is often found that bubonic plague is accompanied by septicæmia; inflammatory enlargements of the deep lymphatic glands may be found in septicæmic plague. This is due to the fact that plague is essentially a septicæmic disease and towards the end of an attack of every form of plague the bacilli are present in enormous numbers in the blood. Crowell recognises only a primary bubonic and a primary pneumonic plague and classifies the bubonic group into (1) uncomplicated cases, (2) bubonic plague with early septicæmia or without superficial buboes, (3) bubonic plague with secondary pneumonia, (4) bubonic plague with secondary meningitis and (5) bubonic plague with secondary cutaneous lesions. The degree of involvement of the lymphatic glands and the invasion of the blood stream are dependent on the resistance offered by the tissues of the patient to the bacilli. These morbid processes have no relation to the virulence of the infecting strain as freshly isolated human strains have been found to possess a uniformly high virulence. The usual mode of infection in bubonic plague is through the skin by the bite of the infected flea but direct infection may also occur. A local reaction at the site of infection is rarely met with. The tonsils sometimes may be the site of entry of the bacilli.

The lesion of bubonic plague consists of a primary bubo at one of the usual sites—inguinal, axillary or cervical and with it may be associated a bubo affecting the nearest proximal group of glands. Secondary buboes appear as a result of infection of other glands by the blood stream. The widespread hæmorrhages and degenerative changes in the tissues are due to absorption of toxin. Bacteraemia is

present in a large number of cases of bubonic plague; it increases until death takes place but may decrease or show fluctuations. In some cases bacilli may be found in the urine.

In rare instances the bacilli have been found to persist at the site of the primary bubo for a considerable time after an attack of plague. In this condition the patient may walk about and recover completely. These carriers when attacked by any specific infectious disease, such as measles or influenza, may show the bacilli in the blood and thus may be a source of spread of the infection by means of plague-carrying fleas or by a respiratory complication. Plague bacilli are said to be present in the blood of convalescent patients and even in persons who are in good health, but these statements need confirmation. All persons are susceptible to infection. Considerable protection is afforded by an attack of the disease though a second attack sometimes occurs.

Pneumonic plague. Pneumonic plague may be either primary or secondary. Most authors agree that primary pneumonic plague originates from a case of bubonic plague in whom a secondary plague pneumonia has developed. Numerous investigations in this connection show that the lungs are secondarily involved in a considerable percentage of cases of bubonic plague. The lung complications frequently occur when the primary bubo is situated in the axilla or neck. Other possible modes of origin of primary plague pneumonia have also been suggested. In severe septicæmic cases associated with flea-borne infection, the bacilli are present in enormous numbers in the expectoration from the lungs, and the droplets of sputum from these patients transmit the infecting agents to persons in contact with them. The Plague Research Commission found that the urine of septicæmic patient killed a guinea-pig when administered subcutaneously. They comment on the risk of contracting primary pneumonic plague from the spraying of bacilli in the air while the patient is micturating. In spite of the fact that the percentage mortality in bubonic type is high, it is remarkable that India is free from pulmonary plague. A suggestion has been put forward that plague bacilli alone cannot cause widespread epidemics of pneumonic plague, and that a symbiosis of *Past. pestis* with other micro-organism is essential. This view, however, has not received support. The sequence of events in the origin in an epidemic of pneumonic plague is that the first case of primary plague pneumonia originates from a case of secondary plague pneumonia, and the subsequent outbreak of primary pneumonic plague from this make up the epidemic. Under average conditions only a small percentage of those exposed to risk are attacked by a primary plague pneumonia. The chance of infection is determined by such factors as overcrowding, bad ventilation, social habits and customs which favour the transference of the infection.

The spread of pneumonic plague is by droplet infection. A vigorous cough may emit droplets to a distance of several yards. The time of exposure of persons to droplet infection is an important factor in deter-

mining the chances of infection. The possible role of carriers in the spread of pneumonic plague, whether pneumonia is of primary form or secondary to bubonic plague, has been much discussed. In a secondary plague pneumonia the bacilli may persist for some time after convalescence, but there is no evidence that they are the source of spread of primary pneumonic plague. The carrier in an epidemic of primary pneumonic plague is a negligible factor in its spread. Similarly, sick rooms and houses are not infective apart from the plague patient, and it is unlikely that dust plays any part in spreading the infection. Overcrowding in badly ventilated house, is perhaps the most important factor. Close contact and neglect of precautionary measures against droplet infection greatly increase the risk. In some cases infection is conveyed by kissing or it has followed a meal of vel rodents. Many authors have stressed the influence of a cold climate in the origin of pneumonic plague, though it is certain that such outbreaks can also arise in hot dry weather. In ambulatory patients or patients suffering from bubonic plague, travel or other exertion may lower the power of resistance of the individual in such a way that it may light up a septicæmia or lung complication.

The organism. The causative organism of plague is a bacillus, *Past. pestis*, discovered independently and almost simultaneously by Yersin and Kitasato in 1894. Plague bacilli appear as an oval rod with convex sides and somewhat rounded ends. The bacilli are mostly bipolar and are generally extracellular. They are easily killed by exposure to sunlight; exposure for one hour to dry heat at 100°C. kills the bacilli when dried on a slide. The bacilli are however very resistant to the action of cold. Bubonic plague can be reproduced in rodents and monkeys by experimental inoculation with cultures of the organism. Pneumonic plague has also been produced in rats and marmots through inhalation of cultures of *Past. pestis*. In rats subcutaneous injection or suspension of infected tissues causes death within seven days and intraperitoneal injections causes a rapidly fatal septicæmia; infection by the mouth and conjunctiva can also be produced. Guinea-pigs are highly susceptible, dying in 2 to 5 days after subcutaneous inoculation, and in 24 hours after intraperitoneal injection with development of purulent peritonitis and septicæmia. Mice are susceptible to the usual modes of infection.

The normal virulence of the plague bacilli when tested on animals, is of a high order, but is subject to variations both under natural and experimental conditions. Freshly isolated strains are invariably virulent. A culture which is avirulent for the rat may be pathogenic for the guinea-pig and strains that have lost a part of their virulence may regain it by passage through susceptible animals; some strains, however, may fail to respond. Many attempts have been made to reduce the virulence of the plague bacillus. Rowland found that growth of *Past. pestis* in normal rat serum depressed its virulence, and growth in fresh horse serum had the same effect, but growth in the inactivated serum raised

the virulence. There is thus evidence that the virulence of the organism varies.

Rôle of the rat and other rodents in plague. The rat plays a part in the epidemiology of plague and it has been found that most of the epidemics of human plague coincide with epizootics in these rodents. The principal species which harbour the infection are *Rattus norvegicus* and *Rattus rattus*. The Indian Plague Commission showed that epidemic first appeared among the rats belonging to the species *Rattus norvegicus*; after an interval of about 10 days an epizootic appeared in the rats of the species *Rattus rattus* and the human epidemic broke out after a further interval of about 10 days. During the off-season (June to December) in Bombay plague persisted in *Rattus norvegicus* and flared up at the onset of the cold weather. The natural mode of infection of these rodents appears to be from rat to rat by contact in the absence of the fleas. In certain rats the disease has been shown to exist in a chronic form. During the height of an epizootic of plague the lesions are those of acute plague but subsequent to this period numbers of healthy rats may show atypical lesions. These rats are said to act as chronic carriers of the disease, serving to keep alive the infection from one epizootic to the next. Though this view has not been accepted by the Indian Plague Commission, evidence has been recorded to show that in this way the disease remains endemic.

Other rodents are also known to harbour the infection and may be responsible for the introduction and spread of plague. In Mongolia and certain districts of Southern Russia, epidemics are associated with the occurrence of plague in a species of marmot called the 'tarabagan.' Possibly the disease is transmitted to man by the fleas which infest these animals, and also lice may convey the infection from one tarabagan to another. Another incriminated rodent is the spermophile or suslik, species of which have been found to harbour the plague bacillus. Nikanoroff reported that in Southern Russia, measures taken to exterminate these animals on a large scale, proved very successful, one such area formerly affected with plague remained quite free from the disease. Similarly, other rodents, such as the gerbille or gerbil and the multimammate mouse have been found to be infected with plague, by several observers in South Africa. In certain parts of California, ground squirrels have been found to be infected. Several cases of human plague were traced to contact with these animals as the fleas infesting them readily attack men.

Rôle of flea in plague. It has been demonstrated that plague is communicated to the rats by the agency of certain fleas as it is known that it is never communicable from animal to animal by simple contact. Chief among these are *Xenopsylla cheopis* and *ceratophyllus fasciatus*. Yersin in 1894 found that the dejecta of flies fed on infected organs of diseased animals showed plague bacilli. Simond was successful in infecting a mouse with plague by injection of an extract of

crushed fleas taken from a plague rat, and several other workers, later on, conveyed plague from rat to rat by the agency of fleas. The second Indian Plague Commission established the rôle of the rat flea in the transmission of plague and showed that if fleas are excluded, healthy rats will not contract the disease. The fleas that have left the body of an infected dead rat convey the bacillus and in the absence of their specific hosts both of these types of fleas bite human beings.

The bacillus multiplies in the stomach of the fleas and is then passed out in the faeces; the period during which fleas may remain infective depends on several factors. In Bombay during an epidemic the fleas remained infective for about 15 days, but during non-epidemic season for 7 days. Under laboratory conditions the fleas may remain infective for 47 days. A low temperature of about 50°F. and a nearly saturated atmosphere are most favourable for the survival of the bacilli in the flea. It has been found that as the cold weather arrives in Bombay the fleas increase in number and the epidemic among rats and man starts during this period. At the onset of hot weather the flea population decreases and plague in rats and man comes to an end. During the off-season sporadic plague cases occur in rats and also in man but the conditions are not favourable for its spread. In other parts of India the incidence of plague depends upon climatic and other factors. Where these conditions are unsuitable, plague either does not occur or runs a restricted course. Madras, on account of a high mean temperature prevalent throughout the year, is relatively free from plague. Another possible cause is that the predominant flea in the Madras Presidency is *X. astia* which is a far less effective carrier of plague than *X. cheopis* or *X. fasciatus*. The Indian Plague Commission showed that a rise of the rat epizootic and consequent outbreak of the human epidemic depends on three factors, (1) a suitable mean temperature between 50°F. and 80°F., (2) presence of rats, and (3) rat fleas. This is the reason why 75 per cent. of plague cases in India are distributed over the Punjab, the Bombay presidency and the United Provinces. In Egypt optimum temperature for an epidemic to occur has been found to vary between 68°F. and 77°F., a condition favourable for the development of fleas. Besides the rat fleas, the rôle of the human flea in the propagation of plague from man to man has been recognised and may be the cause of the outbreak of an epidemic in certain localities.

Laboratory diagnosis. For bubonic plague, the bubo is punctured with a hypodermic syringe and some juice extracted. A thin film is prepared from it and stained by Gram's method, methylene blue or thionin blue; Gram negative bacilli which have a tendency to stain more intensely at the poles, suggest *Past. pestis*. For cultural examination inoculate (at 25°C. and not at 37°C.) both blood agar plates (pH 6.8 to 7.2) and broth tubes. On blood agar the colonies of *Past. pestis* are sticky and can be pushed along the surface; in broth culture chain formation may occur. The definite test for plague is however by

inoculation of the material into animals; two white rats and two guinea-pigs should be inoculated both subcutaneously (one of each variety) and by rubbing some of the material on the dry shaved abdomen (one of each variety). In positive cases the animals die in 3 to 5 days, and on autopsy characteristic lesions will be found with the bacilli in large numbers in the spleen, lymphatic glands and blood. In the pneumonic type of plague, specimens of sputum should be examined in the same way as described for bubonic plague. Animal inoculation should be performed with the sputum, but as other virulent organisms may be present in the sputum simultaneously the best results are obtained by inoculation of the nasal mucosa and conjunctiva which allow plague bacilli to pass through. In septicæmia the organisms can be isolated from blood culture; in all cases of plague blood culture gives positive results just before death.

Prophylaxis. The prophylactic measures in plague depend upon the type of infection. In pneumonic plague it is the human patient and not the rat which is to be considered. The infection is spread by the droplets of sputum laden with the plague bacillus and persons entering the room of the patient, the nurses and the attendants are liable to contract the disease. Persons who have been in contact with pneumonic plague patients should be separated and systematic medical examination made. The quarantine period should extend for seven days after the last contact with the plague patients. Physicians and attendants attending cases of plague should be protected by bag-like masks or by several layers of gauze and cotton wool applied over the face and neck. In China special costumes are worn which prevent infection.

In the case of an outbreak of bubonic plague it is almost solely the rat and the rat flea which are responsible for the propagation of the disease. The rat contracts the disease, enters a house, and dies; then the harboured fleas leave the dead rat and feed on man. The infected flea either introduces the bacilli into the wound caused by the bite or bacilli may be rubbed into a small superficial wound on the skin by the clothing, etc. In some cases bed bugs and other insects have also been suspected as transmitting agents.

Rat destruction. Rat destruction has been considered one of the most important items in the prophylactic measures. Experience has however shown that it is an expensive and tire-

some procedure on account of rapid breeding of this rodent. In Kenya Colony it has been considered a failure, while in India Dennys thinks that this procedure is a useless waste of money as an anti-plague measure. Various other workers however report that rat destruction, vigorously conducted, quickly exterminates plague. The first measure in rat extermination is the disposal of garbage; no article of food should be left accessible to the rat. Various rat-proof houses have been prepared in endemic areas.

The methods of destroying rats with chemicals are numerous. Phosphorus paste made up with glucose can be spread on pieces of bread; strychnine and arsenic if used are placed in boxes which are large enough to allow the rats to get in. Barium carbonate is considered to be a safe rat poison. Kunardt (1920) found that 3 gr. doses of barium carbonate in flour was much more effective in killing rats than other poisonous drugs, and was not poisonous to man. Fumigation of houses and other infected places with sulphur dioxide, carbon monoxide and hydrocyanic acid, has also been practised, but the last two are very dangerous. Many workers, during plague epidemics have tried to exterminate rats by impregnating bread or their bait with bacterial cultures. The best known of these organisms are the *Danysz virus* which is closely related to *Salmonella enteritidis* and brings about fatal infection in rats, their use has now been abandoned.

In India, Tewari and Lall (1925) recommend a method which they consider better than fumigation of houses for the extermination of rats. They use a mixture of potassium chloride 2 dr., potassium nitrate $1\frac{1}{2}$ dr., sulphur 2 dr., powdered and mixed with 5 dr. of mustard oil or castor oil, to which are added 1 dr. of red pepper and a handful of crushed dried neem leaves. This is placed in rat holes over a 9 inch wick of cloth soaked in a saturated solution of potassium chlorate and ignited, the holes being closed.

Besides these, careful inspection of cases should be made in a plague infected area. Houses that have had one or more cases of plague or in which infected rats have been found should always be disinfected to kill rodents and insects. Rat-proof

houses are efficient permanent protection against these rodents. All possible precaution should be taken to prevent contamination of grains and cereals. Various measures have also been directed against fleas. Cresol emulsion, carbon tetrachloride and naphthalene are flea poisons, but they have little penetrative power. Sulphuretted hydrogen is a good pulicide and will kill fleas in 1 per cent. concentration. In plague-infected ships, such substances as sulphurous acid gas, generator gas and hydrocyanic acid gas have been used as disinfectants, the last-named being considered very effective.

Vaccines. The use of vaccine for prophylaxis during epidemics has given encouraging results, Haffkine's vaccine being chiefly used. The protective value of this vaccine is difficult to assess. According to the Indian Plague Commission inoculation diminishes the incidence of attacks, but is not an absolute protection against the disease; mortality among the inoculated is said to be markedly decreased. The protection afforded by inoculation lasts for several weeks, possibly for months. (See vaccine therapy).

Treatment. In the treatment of plague, all attempts should be made to relieve symptoms. In the septicæmic form, treatment should be directed on the same lines as for an acute infectious fever. The asthenic tendencies of the disease should never be lost sight of and stimulants are indicated to resuscitate a sinking patient.

During the early stage, headache and pain can be relieved by proper hydrotherapeutic measures. An ice cap on the head and sponging of the body are very safe and efficient methods for lowering the temperature. Antipyretic drugs should better be avoided. Vomiting is often a troublesome symptom which can be relieved by calomel and a saline purgative; a mustard plaster over the epigastrium is also useful. Morphine is by far the best drug to produce sleep or chloral and potassium bromide may be used. In violent or very restless cases hyoscine is of service. Cardiac weakness manifests itself early in the disease. Hence cardiac stimulants may have to be frequently prescribed.

For the local treatment of buboes, hot fomentations of carbolic acid are useful. They should not be opened or

excised, as excision may often be followed by serious results. Indolent bubonic swellings are treated with iodine liniment. Injections of solution of iodine directly into the bubo have also been recommended. Another preparation that has been advocated is a mixture of iodine and a solution of camphor and thymol in equal parts; this is injected into the bubo in doses of $\frac{1}{2}$ to 1 c.cm. During convalescence tonics are indicated. Patients should be isolated for at least four weeks after the temperature is normal.

Anti plague serum. The use of this serum according to some, offers the best means, at present, of combating this disease. Others consider it of doubtful value. The Indian Plague Commission, from the results of the therapeutic uses of this serum, concluded that no appreciable benefit is conferred by its use. Favourable results have however been obtained when the serum is given early and in large doses intravenously. The problem of specific serum therapy in plague is likely to remain a subject of controversy until further research has determined the essential elements in the serum, whether antibacterial or antitoxic, and how they may be measured.

Bacteriophage. This form of treatment has been tried by d'Herelle and Naidu and his colleagues, but it has not so far proved effective.

Drug treatment. The treatment of plague with chemicals is far from satisfactory. Various chemotherapeutic agents have been tried but none has so far proved effective. Caius and Naidu (1927) in a study of the chemotherapy in bubonic plague recorded their observations on the bactericidal action of antiseptics on *Past. pestis*, and the effect of some of them on plague infected animals. Phenols, mercurated phenols, phthaleins and dye-stuffs were used and many of these had strong bactericidal action *in vitro*. But none of them were effective *in vivo*; mercurochrome, though active *in vitro*, had no influence on plague in rats, and so also resorcinol and mercurated trypan blue. Among other agents, intravenous injections of iodine have been advocated but they are not effective. Mercurochrome has been tried in the septicæmic form. Balfour (1925) suggested its use in plague, beginning with 20 c.cm. of a 1 per cent.

solution intravenously and increasing gradually in subsequent injections. Neo-salvarsan and Bayer 205 have been tried with inconclusive results. Nothing like a really curative treatment of plague is known.

UNDULANT FEVER

It is a long-continued febrile disease characterised by a series of pyrexial attacks with intervening periods of apyrexia. The fever resembles typhoid fever, and there is constipation, muscular pain, anæmia and enlarged spleen. The course of the fever is a protracted one and may last for 3 or 4 months.

Undulant fever is caused by two different but closely related groups of organisms, one the *Br. melitensis* and its serological variants the paramelitensis, the other the *Br. abortus*. *Br. melitensis* causes primarily an infection in goats and is transmitted to man through their milk. Because of its relative frequency in Malta, the fever is also known as Malta- or Mediterranean fever. *Br. abortus* was discovered by Bang in 1897 as the causative organism of epizootic abortion in cattle; it occasionally gives rise to the so-called abortus fever in man. This condition is indistinguishable from Malta fever and these fevers are referred to as undulant fever.

Brucella melitensis infection. Bruce (1887) first isolated the causative organism from the spleen of Malta fever cases. Injections of pure cultures of the organism give rise to a similar disease in the monkey. Inoculation of cultures into man has also been followed by the characteristic symptoms after an incubation period of from five to fifteen days. The present knowledge of the spread of the disease and the value of the prophylactic measures in the control of undulant fever have been greatly widened due to the work of the British Commission for the investigation of the Mediterranean fever (1905-07). All evidence now sustains the view that drinking of raw goat's milk is the paramount source of infection; the disease may also be transmitted by eating butter or cheese made from infected goat's milk.

Brucella abortus infection. Bang (1897) demonstrated that the presence of a small Gram-negative bacillus in the uterine exudate of the cow was the cause of infectious abortion in cattle. The intravaginal injection of this organism into pregnant cows gave rise to abortion and the organism could be recovered from the uterine exudate. It has been shown that a large number of cases of undulant fever are caused not by infection with *Br. melitensis* but with *Br. abortus*, infection being

conveyed by cow's milk. Clinically these cases are characterized by typical undulant fever, but more frequently by irregular fever or fever of a paroxysmal type. The mode of infection in these cases is through drinking the milk of an infected cow or by contact with a diseased animal. Some cases are reported where the persons have been in contact with aborting cows. Agglutinins may be present in patients' serum active against *Br. abortus* up to a titre varying between 1 in 80 to 1 in 5,120. The organism can also be found in the blood.

Laboratory diagnosis. The blood culture gives positive results in early cases (from the second day onward) and is successful in about 80 per cent. of cases. The technique is the same as that for typhoid fever but it is necessary to take more blood (about 10 c.cm.) into either 1 per cent. glucose broth or better into liver broth. Since it is not possible to know what type of organism may be the infecting agent, it is essential to make cultures in duplicate, one under aerobic condition (for *Br. melitensis*) and the other in reduced oxygen tension (20 per cent.) with the addition of 10 per cent. CO₂ (for *Br. abortus* which is very difficult to isolate and the growth of which is dependent on special atmospheric conditions). The organisms are often slow in growing and hence for *Br. melitensis* 7 to 10 days should be allowed before the culture is considered negative, and for *Br. abortus* several weeks (6 or more) should be allowed. A simple method of diagnosis is by the agglutination test. In the blood of normal persons agglutinins may be present for these organisms up to a titre of 1 in 50 (very rarely in 1 in 100). This increase in normal agglutinins is more marked in farmers and veterinary surgeons who come into close contact with infected animals. In patients suffering from undulant fever agglutinins appear about the tenth day of illness and the titre varies between 1 in 100 to 1 in 3,000 but about 20 per cent. of cases of undulant fever fail to show agglutinins. Diagnosis can also be assisted by doing an intradermal test with 1/10 c.cm. of the filtrate of a twenty days' broth culture. A positive reaction consists of a raised plaque 4 to 6 mm. in diameter and occurs about the 7th to the 10th day of the disease. The complement-fixation test is nearly always positive during the course of the disease and often for a long time afterwards. Although infection with *Br. melitensis* and *Br. abortus* are different in their epidemiology and pathogenicity, there is no marked distinction in laboratory diagnosis. *Br. melitensis* is aerobic and can be cultivated more easily while *Br. abortus* is anaerobic; guinea-pigs are insusceptible to moderate doses of *Br. melitensis* while monkeys are very susceptible.

Prophylaxis. *Malta fever.* In such a chronic and debilitating disease as undulant fever, prevention is the only method of controlling it, the treatment being far from satisfactory. As goat's milk is the principal source of infection to man a rigid ban on its use should be enforced. The health authorities

in Malta ordered the killing of all the infected goats in 1909. Concurrently with this the fever incidence fell from an annual average of 632 to 318 among the civil population. The recommendations of the Malta Fever Commission in this connection are (1) examination, segregation and slaughter of all infected animals, (2) examination of the milk of all infected goats for the presence of *Br. melitensis* and of agglutinins in serum or milk. It must at the same time be borne in mind that infection may occur in man in other way and that certain products of milk such as cheese, butter, etc., may also convey the bacilli. In endemic areas the milk should always be sterilised by boiling or only pasteurised milk and cream should be used. In addition to these, as a precautionary measure in endemic areas, the drinking water and food should receive special attention. The urine and fæces of the infected individual should be disinfected; laboratory workers and the nurses attending cases of undulant fever should be particularly careful.

No efficient vaccine is as yet available for the prevention of infection either in man or animal.

Br. abortus infection. The elimination of infectious abortion in cattle is a matter of difficulty. All the animals should be tested by the agglutination or complement fixation test. In a mildly infected herd those showing a positive reaction should be segregated. As the uterine discharge of the infected animals is infectious, all measures should be adopted for the isolation of the animal and disinfection of the stall. For prophylaxis of animals vaccines prepared from living organisms have been found to confer some degree of protection; heat-killed organisms have less protective power and dead bacilli are useless in this respect. It must be remembered that vaccines should never be used except in badly infected herds, otherwise the infection is spread rather than checked. Reports of the successful vaccination of man against *Br. abortus* infection have been published (Nicolle and Conseil, 1922; Burnett, 1924), but they are not very convincing. Recently, Dubois and Sollier (1930) prepared a vaccine using various strains of *melitensis* and *abortus* for prevention of infection in persons engaged in dealing with infected animals. The first injection is of 0.25 c.cm. containing

500 million organisms, the second of 0.75 c.cm. and the third of 1 c.cm. As a result of the full course of injections given to 111 persons engaged in dealing with infected animals, none developed undulant fever while two of the 36 controls developed the disease.

In spite of the fact that in an endemic area a large proportion of the milk supply is contaminated there are apparently very few cases of undulant fever recorded. This may be due to non-recognition of the disease, the cases recorded representing only a fraction of those actually occurring. In addition it is probable that immunity to infection may occur without recognisable clinical disease. Thus immunity might be acquired in infancy from drinking infected milk and maintained for a considerable time afterwards, till a lowering of the individual's resistance due to some other cause opens the door to infection. In endemic centres or in the face of an epidemic the general health should be preserved and the use of raw milk forbidden.

Treatment. The results of the use of drugs in the treatment of undulant fever have not been encouraging. It should be remembered that undulant fever is of prolonged duration and the treatment necessitates a careful management of the case during the illness.

In view of the constipation in this disease, it is well to use some mild purgative such as calomel in the beginning; hydrotherapeutic measures have to be carried out to control hyperpyrexia; antipyretic drugs such as quinine, phenacetine, etc., are not called for. The protracted course of the disease makes it necessary to conserve the vitality of the patient by rest and nutritious diet.

Drug treatment. Intravenous injections of various metallic compounds have been tried. Mercurochrome in doses of 0.2 gm. has been tried apparently with good results; intravenous injection of 10 per cent. solution of collargol in doses of 2 to 4 c.cm. has also been advocated. Conterno (1930) used a 2 per cent. solution of trypanflavine in doses of 10 c.cm. injected intravenously with two days' interval for 8 to 10

injections. Of the 14 cases treated ten were followed up for several months ; six were cured straight away and three required a further course of 3 or 4 injections. Thusber (1930) treated 7 cases of undulant fever with acriflavine hydrochloride, keeping seven others as controls. The dosage employed was 0.1 gm., 0.2 gm., and 0.3 gm. at intervals of three days along with 20 c.cm. of saline intravenously. In five of the treated cases the fever was arrested within one month of the treatment while in untreated cases the fever continued for 9 months to 2 years. Rudnew and Krumberg (1931) after failing with different forms of treatment, finally utilised X-ray therapy, the region of the spleen being irradiated for fifteen minutes on five or six occasions. Neo-salvarsan, colloidal gold, compounds of silver with methylene blue have also been tried, but definite evidence as to their therapeutic value is lacking.

Vaccines. Favourable results have been reported by various injections of vaccines. The initial dose for sensitized vaccine is 250 million organisms progressively increased every two or three days and for autogenous vaccine 50 million organisms, progressively increased at three day intervals, to 200 million organisms. Though vaccines are reported to be successful in the treatment of undulant fever their value has not yet been established.

Autoserotherapy has also been tried with variable results. It was found by Partearroyo that 60 per cent. of the goats suffering from the disease gave a positive agglutination reaction. He reported favourable results with 50 to 60 c.cm. of antiserum, and this method of treatment is worthy of further trial.

OROYA FEVER AND VERRUGA PERUANA

Oroya fever is an acute infectious disease caused by *Bartonella bacilliformis*. Verruga peruana is characterised by the development of nodular eruptions on the skin and mucous membrane resembling those of yaws. Both the diseases are now recognised as different manifestations of one and the same disease, the trend of opinion being that Oroya fever is the first stage of the illness, eruption occurring in the later stage if the patient survives an attack. Strong and his colleagues

(1915) however failed to produce typical Oroya fever in man after inoculation of the material from verruga lesions and they considered the two diseases as distinct entities. The work of Noguchi (1926) fully established the fact that the two diseases are but different manifestations of one and the same infection. He was successful in cultivating *B. bacilliformis* from the blood of a patient suffering from Oroya fever. Intravenous injection produced remittent fever in monkeys, and verruga-like lesions appeared after inoculation with the cultures; the character of the infection depended upon the virulence of the infection and susceptibility of the host.

Lowoff and Vancel (1931) on the other hand have shown that there are two organisms concerned in these infections, the one, *Bartonella bacilliformis* is responsible for verruga lesions and the other *Eperythrozoon noguchi*, is the cause of Oroya fever. They believe that the reason why cultures from the blood of cases of verruga or Oroya fever produce verruga only in monkeys is due to the fact that *Bartonella* can be cultivated whereas the eperythrozoon cannot be cultivated. Other workers, however, support the view that verruga and Oroya fever are different manifestations of the same disease. *Bartonella* can be observed in the red cells in cases of verruga and also in cases of Oroya fever and the eperythrozoon has not been observed in the blood of man.

The disease is considered to spread by a kind of phlebotomus especially *P. verrucarum* and also *P. noguchi*, and *P. peruensis*, though it was earlier thought to be conveyed by a tick.

Prophylaxis and treatment. It has been suggested that a species of phlebotomus is the transmitting agent. Prophylactic measures, therefore, rest on destruction of these sandflies. There has so far been no satisfactory method of treatment. With regard to the nodules of verruga peruana it may be said that they should be kept scrupulously clean so as to prevent secondary infection. The curative influence of X-rays on the various skin lesions in man suggested its application in this disease. Muller and Tyler (1930) showed that early verruga nodules when exposed to a single properly graduated dose of X-rays are inhibited in their growth. This justifies a trial of X-rays in suitably graduated doses in treatment of verruga nodules in man. Oroya fever should be treated on the same lines as for infectious fever. Intravenous injections of salvarsan are said to give beneficial results.

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CHAPTER V

REMEDIES USED AGAINST LEPROSY

Leprosy is a disease exceedingly difficult to treat, but it should nevertheless be emphasised that it is a remediable disease. There is no specific remedy for the disease yet available. The methods of treatment at our disposal, however, if properly carried out, can cure quite a good proportion of the cases and there is no reason why lepers should be considered incurable and be shunned.

This dreaded disease is prevalent in many of the tropical and sub-tropical countries. The number of lepers in the world is estimated to be about three millions, but, according to Muir, when the incipient cases are taken into account, the number is very much larger. Rogers states that there is a remarkable relationship between high leprosy incidence and high rainfall, especially in not tropical climates. The only tropical areas with little or no leprosy are those with the extremely low rainfall of under 10 inches. It is suggested that abundance of biting insects in humid regions may cause punctures of the skin of man favouring the entrance of lepra bacilli derived from contact with cases of the disease. Further, damp heat is likely to favour the temporary survival of the bacilli outside the human body and in this way infection is favoured. According to others sparse populations connected with low rainfall are responsible for the low incidence and not the climatic factor.

Recent work on rat leprosy has thrown valuable light on this subject. Although the bacillus of rat leprosy is difficult or impossible to cultivate, one rat can be easily infected by fresh material obtained from another suffering from the disease. The infective material can be kept active outside the body for months. The extraordinary number of lepra bacilli in the nodular lesions of the skin and nasal mucous membrane is accompanied by little effect on the general health for long periods. This shows the low toxicity of the organism in its intact and acid-fast coating. In some phases of the disease local inflammatory and general constitutional reactions (e.g., fever) may occur. In the nerve type the bacilli may be very few in number; they are found either in the fibrous tissue of the nerve trunk or round its terminations in the skin. In this type the resisting power of the tissues is greater and the disease may die out.

Leprosy is not a hereditary disease. The disease is contracted chiefly by intimate contact, e.g., staying in the same house with a

leper. Healthy persons, as a rule, do not get it; leprosy cannot be considered to be a highly contagious disease. The first two decades of life are the periods when one is most liable to infection, adolescence and the commencement of sexual life are said to lower the resistance to the disease. Children are more susceptible than adults. The incubation period may vary from a few weeks to many years. It may be stated, however, that it is very difficult to form any accurate estimation regarding the incubation period of this disease, as the latter may exist for years without attracting any attention. The incubation period depends on the degree of reaction of the tissues to the infective organism and on the general health of the individual. A delay of six months in the segregation of children born to lepers renders them liable to get the disease. The children in the first 2 or 3 years of their life are more susceptible to the disease. The nodular cases with numerous bacilli are more infective than the nerve leprosy with very few organisms.

The disease is seen in two main types which may co-exist. These are the neural type and the cutaneous (or nodular) type. In both types there are seen various phases, described by Muir as (1) the quiescent stage, during which the bacilli may multiply and the lesions extend locally but there is no toxæmia; (2) the reactionary or inflammatory stage, during which the lesions become inflamed and general toxæmic symptoms appear; and (3) the phase of resolution, following upon the subsidence of reaction.

The primary lesions are most frequently seen on extensor surfaces of the limbs and on the more exposed parts of the body such as the cheeks, outer surfaces of the shoulders and arms, the buttocks and outer surfaces of the thighs. The parts less commonly affected are the flexor surfaces, the neck, middle of the body and soft unsupported part of the abdomen. All these point to contact infection. There is little evidence that the organisms are inoculated by insects. Recent evidence is against the primary nasal infections. Investigation of the primary lesion has shown that in 14.6 per cent. of cases are of the depigmented anæsthetic type,—maculæ; in 11.9 per cent., of erythematous red type; in 9.5 per cent., of non-anæsthetic type; in 5 per cent., there is paralysis; in 3.5 per cent., there are ulcers and erythematous anæsthesia.

Diagnosis is easy in a well-developed case. Bacteriological examination of the skin shows many acid-fast bacilli, but in nerve leprosy, bacilli may be very few or undetectable, and diagnosis has to be made on clinical grounds alone. If the acid-fast bacilli cannot be found in the nodules of the skin, the nasal mucosa should be examined. In early cases thickening of nerves such as the ulnar, peroneal, great auricular and other superficial nerves may be looked for. Erythematous patches, papular eruptions, and blisters appearing now and then on different parts of the body, depigmented patches, porokeratosis, hyper-

æsthesia, thermal anæsthesia, repeated febrile attacks are some of the symptoms.

Attempts have been made to diagnose leprosy by means of a specific allergic reaction by using a suspension of the leproma. This test is known as the 'leprolin test.' Muir adopts the following technique in preparing leproma suspension for the leprolin test. After sterilising the skin, a portion of the tissue of the thickened pendulous ear lobe is removed with a sharp knife and placed in a petri dish. Several pieces of tissue are removed in a similar manner from other patients. These are boiled in water for 45 minutes and then cut up into small pieces, which are dried for a few hours under a fan and thereafter in a vacuum dessicator over pure sulphuric acid. The dried material is ground up to a fine powder in a glass mortar and stored in a dessicator. In preparing the suspension, 0.4 gm. of the dry powder is ground up with about 10 c. cm. of saline; the fluid suspension is pipetted off; the solid residue in the mortar is again ground up with saline, and the fluid suspension pipetted off and added to the rest of the suspension, this process being repeated three or four times. The whole suspension is then shaken up in a large test tube and allowed to sediment for 10 minutes, after which the fluid is again pipetted off, the sediment being discarded. Saline is added to make 100 c.cm. along with 0.5 per cent. carbolic acid. The suspension is then standardised and made up in 1 c. cm. ampoules which are sealed and heated at 120°C for half an hour. This forms Hansen's (H) leprolin.

A control leprolin is prepared by the same method. The spleen and liver of a rat which had been inoculated intra-abdominally with rat leprosy 5 or 6 months previously, are used in place of the lepromatous skin. This forms the Stefansky (S) leprolin.

The usual dose used for inoculation is 0.2 c. cm. of this suspension intradermally.

A positive reaction is indicated by the appearance, several days later, of a red flush with a raised area round the point of inoculation. In severe reaction there is desquamation, vesication and pustulation. In cases of nerve leprosy with few bacilli, especially in those of the macular type, the reaction to Hansen's leprolin is increased, but that to Stefansky's leprolin remains the same. In cases of cutaneous leprosy with numerous bacilli the reaction to Hansen's leprolin is diminished or absent, but that to Stefansky's leprolin is apparently not diminished. A strongly positive leprolin may be taken as an indication for a favourable prognosis, as it indicates resistance to the infecting organism.

Syphilis, presence of intestinal parasites, malaria, debilitating diseases, improper diet, long residence in hot, moist and enervating climates are potent predisposing causes. Leprosy uncomplicated with syphilis does not give a positive Wassermann test.

Chaulmoogra oil. The oil is obtained from the seeds of various species of the natural order *Bixineæ*. *Taraktogenos kurzii* is a tall, evergreen tree, 40 to 50 feet in height with lanceolate or oblong lanceolate leaves. It grows plentifully in Eastern Bengal and the upper part of Burma and is distributed along the eastern and southern slopes of the Pegu, Yoma, Martaban, in the forests of Sylhet and Chittagong. The fruits, which grow upon the stems and main branches of the tree are of the size of oranges and have numerous seeds embedded in the pulp. The oil is expressed from these seeds.

Chaulmoogra has been used in the treatment of leprosy in Hindu medicine for many centuries and during recent years it has been generally recognised as the most valuable remedy in the treatment of this disease. In the Buddhist literature of ten or more centuries ago, mention is made of the great improvement in the condition of lepers after eating raw chaulmoogra seeds. There are records to show that the oil extracted from the seeds has been used in the treatment of leprosy and as a household remedy for many skin diseases since 1595. In the 'Makhzan-el-Adwiya', one of the oldest books on Mahomedan materia medica, mention is made of the use of the seeds under the name of 'chaulmoogra.' A description of the seeds and their uses is also found in ancient Chinese literature.

In indigenous medicine the oil was administered orally, mixed with clarified butter. Western practitioners quickly appreciated the beneficial effects produced by this drug and began to use it from the very early days of British rule. In 1854, Mouat reported improvement in a case of leprosy as a result of oral administration and local application of chaulmoogra. In 1868, the curative effects of chaulmoogra were so well known that it was made official in the Pharmacopoeia of India, the chief preparation being an ointment which was to be made from the pounded kernels mixed with 'unguentum simplex.' It was not till 1904, when Power and his collaborators published in detail the chemistry of chaulmoogra oils, that the attention of the scientific world was drawn to this valuable drug.

Besides *Taraktogenos kurzii*, certain other trees belonging to the natural order *Bixineæ* also yield oils having a composition closely akin to that of true chaulmoogra oil. *Hydnocarpus wightiana* is one of the most important members of this group. It grows abundantly in the western parts of the Peninsula from South Konkan along the coastal range. *Hydnocarpus anthelmintica* is another member of the same family. This tree is indigenous to Siam, Northern Cochin and Gamboja. *Hydnocarpus wightiana* seeds have recently been planted in different parts of Africa, Malaya, the West Indies, South America and

elsewhere, and the oil is gradually becoming available as the trees develop. There are several other species which have also been recognised as important sources of the oil. In the following table, the names of the most important members with their habitat are given :

Description.	Habitat.
<i>Hydnocarpus venenata</i>	... Ceylon, Deccan and Burma.
„ <i>castanea</i>	... Burma.
„ <i>anthelmintica</i>	... Siam, French Indo-China.
„ <i>curtisi</i>	... Penang.
„ <i>hutchinsonii</i>	... Philippine Islands.
„ <i>subfalcata</i>	... Philippine Islands.
„ <i>woodii</i>	... India.
„ <i>alpina</i>	... India.
<i>Asteriostigma macrocarpa</i>	... Travancore.
<i>Onchoba echinata</i>	Sierra Leone.
<i>Carpotroche brasilliensis</i>	... South America.

In the older literature, it was believed that chaulmoogra oil was derived from the seeds of *Gynocardia odorata* which is a native of Sikkim, Assam and Chittagong. The fruits as well as the seeds are very similar in appearance to those of *Taraktogenos kurzii* and that is probably the reason for the confusion that existed for such a long time, until in 1901, Prain showed that it was a mistake.

The chief sources of oil in India are *Hydnocarpus wightiana* and *Taraktogenos kurzii*. *Hydnocarpus wightiana* grows in gardens and accessible places all over South India, so that seeds can be obtained quite fresh. *Taraktogenos kurzii*, on the other hand, grows in out-of-the-way places where its seeds cannot be gathered easily during the rainy season when the fruits fall. It is therefore not easy to get fresh seeds for extraction of the oil. The oil derived from *Hydnocarpus wightiana* is, therefore, preferred to the other. It is further considered to be superior on account of its higher rotation value (5.5 degrees higher than *Taraktogenous* oil).

Chemical composition. The oil is obtained from the chaulmoogra or *hydnocarpus* seeds by hot or cold extraction. The seeds yield 30 to 40 per cent. of the oil according to the method used. By hydraulic pressure about 30.9 per cent. of the oil is obtained, while by ether extraction the yield is much more and amounts to 38.1 per cent. The oil is of a pale yellow or a reddish brown colour. The oils sold in the market are usually rancid, dark brown and devoid of therapeutic action. The fatty oil has got the following properties :

Expressed oil. Oil extracted by ether.

Melting point	22—30°C.	22—30°C.
Sp. gravity	0.952 at 25°C.	0.951 at 25°C.
Acid value	23.9	29.5
Saponification value	213.0	208.0
Iodine value	103.2	104.4.

On hydrolysis, the fatty oil yields the following fractions:—

1. Total fatty acids, m.p. 44–45°C.
2. Glycerol.
3. Non-saponifiable portion.

The fatty acids are mixtures of several constituents and these can be separated by further analysis, yielding:

- (a) Chaulmoogric acid.
- (b) Hydnocarpic acid.
- (c) Probably some lower homologues of chaulmoogric acid (not definitely isolated).
- (d) Palmitic, linolic acid, etc.

Similar fatty acids are contained in oils from the seeds of *Hydnocarpus anthelmintica*, *H. wightiana* and *H. alpina*. The Philippine trees, *H. venenata*, *H. alcalæ* and *Pangium edulæ*, the South American tree *Carpotroche brasiliensis* and the African tree *Onchoba echinata* also yield oil of a similar nature. The Chinese tree 'Ta-Feng-Tzu' is nothing but *Hydnocarpus anthelmintica*. The following table by Perkins and Cruz gives the composition of the oil obtained from various species.

It will be seen from the table given above that all the species mentioned above contain chaulmoogric and hydnocarpic acid in different proportions. The virtue of chaulmoogra oil has been shown to reside in these two peculiar fatty acids of unsaturated type characterised by the presence of a ring of carbon atoms. Chaulmoogric acid— $C_{18}H_{32}O_2$ —has a melting point at 68.5°C. and is dextrorotatory. Its iodine number is 90.1. Hydnocarpic acid— $C_{18}H_{34}O_2$ —melts at 60°C. and is also dextrorotatory. Its iodine number is 100.2.

Gynocardia odorata has already been mentioned as inactive. A study of its chemical composition shows that the fatty acids derived from it do not contain either of the unsaturated acids which are considered responsible for the special action of chaulmoogra oil. The oil obtained from the market is of a brownish red colour and is very frequently mixed with gynocardia oil and linseed oil. Much of the divergence of results obtained by various workers in the treatment of leprosy in the early periods might be accounted for by the impurity of the oil employed. Taraktogenous oil is costly and naturally there is a great incentive on the part of retail dealers to mix cheap oils with it. The extended use of the cheaper *Hydnocarpus* oil has removed

COMPOSITION OF CHAULMOOGRA OILS
(Perking and Cruz)

Species.	Chaulmoogric acid	Hydnocarpic acid	Other constituents.	Fatty acids M.P. ° C.	Fatty acids specific to dextrorotatory power
<i>Gynocardia odorata</i> (pressed oil) ...	None	None	Gynocardin, linolic, palmitic, linolenic, oleic	..	None
<i>Hydnocarpus alcala</i> ...	Approximate 90 per cent.	None	Palmitic, oleic	59	58·65
<i>Hydnocarpus alpina</i> ...	Indicated	Indicated
<i>Hydnocarpus anthelmintica</i> (pressed oil) ...	Present	Present	Glucoside, oleic, palmitic	42-43	59·6
<i>Hydnocarpus venenata</i> (pressed oil) ...	Present	Present	Glucoside	43	60·9
<i>Hydnocarpus wightiana</i> (pressed oil) ...	Present	Present	Unknown unsaturated acid	41-44	60·4
<i>Onchoba echinata</i> (extracted oil) ...	85·5 per cent.	...	No palmitic, liquid acids 12 per cent. ...	18	8·49
<i>Pongium edule</i> ...	Indicated	Indicated	Unsap. 1·5 per cent. gynocardinpalmitic
<i>Taraktogenos Kurzii</i> (pressed oil) ...	Present	Present	Glucoside, palmitic acid ...	44-45	52·6

this tendency to adulteration to a great extent. Whenever there is any doubt as to the nature of the oil, it is always better to test its purity. Of all the tests, the specific rotation of polarised light is probably the best indication. The specific rotation of *Hydnocarpus wightiana* is 57.7 and that of *Hydnocarpus anthelmintica* 52.5.

Pharmacological action

Bactericidal action. The oil itself has no bactericidal action, perhaps because it does not penetrate the cell wall. The fatty acids present in it are said to possess a destructive action on acid-fast bacteria *in vitro*, but this work has not been confirmed. Recent experiments have shown that even 5 per cent. solution of the fatty acids have little or no effect on the bacillus of rat leprosy or the tubercle bacillus.

Local action. Chaulmoogra oil is irritant to the skin and mucous membranes. Nausea and vomiting are induced even with small doses, such as 3 to 4 drops. Though it is possible to develop slowly a gastric tolerance to larger doses (15 drops), there is no denying the fact that it is liable to set up anorexia and vomiting very frequently. This applies chiefly to impure oil extracted from bazar seeds. Not only the oil but the sodium salts of the fatty acids as well as the esters have pronounced irritant properties though much less marked than the original oil. The hypodermic injection of plain oil in daily doses of 5 c.cm. was found by some workers to produce intense local inflammation and induration. Corbett found that intramuscular injections produced extensive abscesses. According to Muir, if properly prepared oil from fresh seeds is used, such accidents never occur.

The esters have an irritant action. The oil does not appear to be quite so irritant on intravenous injection in man. Harper of Fiji dissolved the oil in ether and used it by the intravenous route in the treatment of his leprosy cases. Plain oil given intravenously produces embolism of the lungs. Intraperitoneal injections produce less local reaction, but after repeated injections a deposit, apparently fibrin, is found over the spleen and liver. Care must be taken in the use of the sodium salt, as it is extremely alkaline.

Systemic Effects. It has been said that chaulmoogra oil does not possess any systemic effect at all. The researches of Rogers, Read and others, however, tend to show that it does possess some systemic effects. Thomas and Muller in 1911 observed narcosis in a few of the animals to which they administered hydnocarpus oil by the mouth. Cats given doses of oil up to 3 gm. per kilo, vomited, and apparently not much of the drug was absorbed. Such a dose is exceedingly nauseating, but the animals developed deep narcosis.

Valenti obtained a preliminary stimulation of the central nervous system followed by paralysis, with the ethyl esters of chaulmoogra oil;

death may result from paralysis of the respiratory centre. Ohara observed a strong central paralytic effect and a lowering of the systemic blood pressure following the administration of the ethyl esters and the sodium salts of chaulmoogra.

Apart from certain gastro-intestinal effects the oil from fresh seeds, when properly extracted and stored, produces very little other systemic action. Irritant and toxic products are formed in the seeds when improperly collected.

Lung embolism. Costel after administering to man the oil hypodermically in daily doses of 5 c.cm. reported fatty embolism of the lung in 2 cases. Walker, McArthur and Sweeney in their chemotherapeutic studies of the action of the ethyl esters of chaulmoogra upon rabbits, reported pulmonary embolism in a large number of animals. Hypertrophy of the lungs, pneumonia and broncho-pneumonia have also been frequently observed by other workers. It is difficult to understand why the lung tissue should bear the brunt of the irritative action of the chaulmoogra derivatives. According to Muir this should never occur in man if the injections are properly given.

Hæmolysis. Hæmolysis is undoubtedly produced by intravenous injections of the sodium salts of chaulmoogric and hydnocarpic acids. With proper dilution of the salts used, this hæmolysis can be reduced to a minimum so as not to entail any special risk to the patient.

Calcium metabolism. According to Read, chaulmoogra oil given orally in small doses produced a marked increase in the urinary calcium and also an increase of faecal calcium. Continued administration, however, reverses the effect and favours calcium retention. Prolonged hypodermic administration of ethyl hydnocarpate in therapeutic doses to dogs decreases the urinary calcium and greatly increases faecal calcium so that there is a hyper-excretion of calcium. In experimental dogs, there is generally found an increase in the blood calcium after the administration of the hydnocarpatates in ordinary therapeutic doses. In toxic doses, on the other hand, a rapid depletion of the calcium-reserve is observed.

Nitrogen metabolism. A definite increase in the amount of nitrogen excreted in the urine after the oral administration of chaulmoogra oil has been observed by Read. This indicates a considerable degree of tissue breakdown. Continued administration of small doses of ethyl hydnocarpate shows progressive decrease in urinary nitrogen and a large increase in the ammonia excretion. This is an evidence of a marked degree of acidosis in the tissues.

Sulphur metabolism. Large doses of the chaulmoogrates given to rabbits, produced a temporary increase in the excretion of all forms of sulphur. The ethereal sulphates show the greatest percentage of

rise and the neutral sulphur is also increased. Repeated doses do not produce the increase seen after the initial dose; in fact, there is a slight decrease.

Therapeutic Uses

Oral administration of seeds. The administration of chaulmoogra by the oral route has been practised since very early days. This method is favoured by some institutions even to this day. At the Rangoon Leper Asylum, the regular treatment was with pills made of *Hydnocarpus* seeds, rhubarb and salt. Travers (1926) used orally the fresh nut of *Hydnocarpus anthelmintica* mixed with *Cannabis indica* and *Tribulus terrestris* and reported 11 per cent. cures. Recently, Cochrane has given a fair trial to this method with slight modifications. Fresh seeds were administered to the patients, taken after meals. The results obtained were not promising and he concluded that the oral administration of the seeds should be confined to cases refusing injections, or to young children who cannot stand injections and to those who live far away that distance prevents them from coming regularly for treatment.

Oral administration of oil. The oil was used by a number of workers. Lebœuf (1900) gave the oil in emulsion in milk, in capsules and salads. Unna (1900) used the oil and to avoid gastric disturbance administered it in the form of keratin-coated pills and also in the form of enemas. Azua used the oil and managed to give gradually as high as 300 drops per day. Denney (1929) has also given the oil in large doses orally in enteric capsules without nausea. Engel-Bey, who had a large experience with leprosy in Egypt, recommends oral administration in dosage of 30 drops of the purified oil solution under the trade name 'Anti-leprol' for a period of 3 to 4 years. Small doses have also been successfully given in pill form.

The greatest disadvantage of oral administration of chaulmoogra, however, is that it sets up gastric irritation and nausea in doses required to obtain therapeutic results. If the patients are able to tolerate large doses by the mouth, the

disease will usually improve. Others argue that if a patient can stand large doses by the mouth, his general health must be good and he is bound to improve in any case. Unfortunately in actual practice one cannot give large quantities to produce permanent results. The method of administration is to commence with 1 to 2 min. in milk or other suitable vehicle, or the drug can be placed in gelatin capsules and given directly after meals. The dose is first given once a day, then increased to 3 times a day. Every other day, the dose is increased by 2 min. until about 100 min. 3 times a day is reached. Seldom, however, can such a large dose be tolerated, firstly because of the vomiting that the drug produces and secondly because in large doses there is a tendency for toxic symptoms to appear, *e.g.*, langour, emaciation, etc. If the dose is persisted on when signs of intolerance appear, fatty degeneration of the organs may set in.

The best results recorded, within recent years, from the oral use of chaulmoogra oil are those of Ralph Hopkins (1925) of the Louisiana Leper Institution. He reported as the result of fifteen years' patient trial, a cure or improvement in 45 per cent. of 82 incipient cases and improvement in 21 per cent. of 38 advanced cases.

The oral administration of chaulmoogra is gradually getting out of the field of therapeutics. The dosage can seldom be increased to equal that of subcutaneous injection of the oil or its esters and cannot therefore be more than a palliative in this obstinate disease. Moreover, according to McDonald and Dean, oral administration with all its disadvantages is unnecessary as the results obtained by this method are decidedly inferior to those obtained by the subcutaneous or intramuscular injections of the oil or its derivatives.

Subcutaneous and intramuscular injection. The use of oil by injection appears to have been proposed first by Tourtoulis of Cairo, who in August 1899, presented the method before the Academy of Medicine and the Dermatological Society of Paris. Costel as a result of his own experience did not regard the method as one for routine employment, reserving it for excep-

tional cases. The method did not find favour for a long time on account of the pain and irritation caused at the site of the injection. An unquestionable advance was the mixture used at San Lazaro Hospital by Mercado and Heiser (1914) which consisted of chaulmoogra oil 60 c.cm., camphorated olive oil (10 per cent.) 60 c.cm., resorcin 4 gm., and ether 2.5 gm. This is mixed and dissolved over a water bath and filtered. The initial dose is 1 c.cm., increased according to tolerance. Good results have been obtained with this mixture by Mercado, Heiser and other workers. Unfortunately as it was for years prepared with crude chaulmoogra oil which is likely to contain larger quantities of fatty acids owing to decomposition, the mixture was very irritating and often caused extensive local swelling, fever and temporary disability. Naturally this militated against its intensive and long-continued use by most patients. As now prepared with refined oil of neutral reaction it is much less irritating and when used intensively seems to be giving results that are not inferior to those obtained with the ethyl ester (to be described later).

Muir has for some years used large doses of *Hydnocarpus wightiana* oil from ripe seeds with 4 per cent. creosote added as an antiseptic, both intramuscularly and subcutaneously under the skin lesion. The cheapness of the drug makes it the remedy of choice for routine use. The advantage of this product is that it is the least likely of all the drugs used to cause severe reactions.

Wilson of Korea has adopted the *H. wightiana* oil injections in preference to the esters, the Korean patients greatly preferring them on account of the absence of pain after the injections and he reports very favourable results from a trial in 300 cases. The cheapness of the whole oil is an additional advantage when a large number of poor patients have to be dealt with.

The only disadvantages of this treatment are firstly the viscosity of the oil and therefore difficulty in injection; warming the oil makes it thinner and facilitates injection. Secondly the quantity to be administered makes the export difficult.

Intravenous injection. In order to obviate the difficulty of marked irritation to the tissues resulting from intramuscular injections of chaulmoogra oil, efforts were made to introduce the drug directly into the vein. Vahram first succeeded in preparing a 'pseudo-colloidal' emulsion of chaulmoogra oil with gum arabic suitable for intravenous injection. The author recommends the first injection to be $1/4$ c.cm. progressively increased by $1/10$ c.cm. until 2 c.cm. have been given. After 20 injections given intravenously, others may be given subcutaneously. Both intravenous and subcutaneous injections may be administered every second day. Harper in Fiji (1921) began to use the crude chaulmoogra oil intravenously in doses of 15 min. daily for 6 days weekly, for months on end without ill effects. Of 40 cases so treated, all except 2 improved. The formula used for intravenous injection consisted of iodine 1, ether 250 and chaulmoogra oil 750.

According to Harper, the dosage may start with 10 min. of the above mixtures for adults and may be increased gradually to 20 min. without ill-effects. This dose is given daily for 6 days a week and may be continued for at least 5 months. Improvement in the majority of cases was recorded.

Sodium salt of fatty acids of chaulmoogra and hydnocarpus oils. Rogers (1916) working in Calcutta was able to obtain different fractions of the fatty acids and tried each one of them orally to find out the true active ingredient amongst them. Trials with gynocardic acid (gynocardic acid was originally mistaken for hydnocarpic acid, the lower-melting point fatty acid of chaulmoogra oil) showed that fractionate oil was better borne than the others and appeared to be more effective than the whole oil which contains a large quantity of almost useless palmitic acid. Gynocardic acid, however, was found to be unsuitable for injection on account of its insolubility. An attempt was made to prepare a soluble compound and in 1915 sodium gynocardate was prepared and several patients were treated with injections of watery solutions of this substance either subcutaneously or intramuscularly.

Sodium hydnocarpate. The results obtained with this salt were promising, but the injections, though much less pain-

ful than intramuscular injection of Heiser's mixture, were still painful. A 3 per cent. watery solution of the sodium salt of the fatty acids was found to be most suitable for injection purposes. Injections were given under the skin lesions on the extremities or body twice weekly in doses beginning with 0.5 c.cm. and increased by the same amount at each dose up to 5 c.cm. or more. The physician should be guided by the reaction produced in the patient as a result of the injection, *e.g.*, fever, general or local reactions in the form of swelling and softening of the skin lesions. When these reactions are manifest, the injections should be stopped for a week and the next dose reduced by 0.5 c.cm. and only increased again when no reaction ensues.

In 1916, Rogers found, by a series of animal experiments, that the same 3 per cent. solution, which was being used for subcutaneous and intramuscular injections, could as well be used intravenously. This finding opened up a new field and it was thought at the time that the great bugbear in the chaulmoogra oil treatment, namely, the question of irritation to the tissues, had at last been solved. A series of successful cases were recorded by him in 1921 by following this method of intravenous administration of sodium hydnocarpate in 3 per cent. solution. The most striking phenomenon with such injections was the occurrence of definite reaction in the diseased tissues, sometimes accompanied by fever. Later on, it was found that a weaker solution of 1 to 2 per cent. was more convenient to use and produced these untoward effects to a lesser extent. The phlebitis and blocking of the vein might be counteracted by adding a 2 per cent. solution of sodium citrate to the injection but even this was not always preventive.* Another way to avoid blocking of the vein is to mix the solution with an equal quantity of blood before injection (Muir 1927). The intravenous method, however, did not gain much popularity in view of the fact that though there was no pain, fibrous adhesions and endo-phlebitis at the site of the injection followed frequently.

Alepol. As it was observed that salts of the higher melting point fatty acids are irritant and painful, Rogers (1927)

used the sodium salts of the low-melting point fatty acids of *H. wightiana* in order to do away with this drawback. In consequence a sodium salt of the low-melting point acids has been prepared under the trade name of 'Alepol' (B. W. & Co.). Dikshit (1932) studied the pharmacological action of this drug. Its toxicity is fairly low. A 3 per cent. solution introduced into the femoral vein of cats or dogs is lethal in doses of about 0.3 gm. per kilo. of body weight. It has a selective action on acid-fast bacteria and inhibits the growth of tubercle bacilli in concentrations as low as 1 in 200,000. It also exerts a toxic action on some helminths like the micro-filaria of crows and tapeworms of cats. It has got a slight depressant action on the cardio-vascular system. Respiration is stimulated by small doses administered intravenously and the bronchioles are slightly dilated. The most important action is however on the erythrocytes. The soap has got marked hæmolytic properties, but this action can be considerably lessened by dissolving the drug in Locke's solution or by using Muir's method for giving intravenous injections of the hydnocarpates. The latter consists in withdrawing blood in the syringe containing the dose, mixing and then injecting the whole quantity intravenously. This reduces the local action on the vessel endothelium and also diminishes the hæmolytic action of the soap on the red blood cells.

This product has the great advantage of being sent out in powder form and after dissolving the amount in distilled water and sterilising, it is ready for use. Because of the ease of export and simplicity in injecting a watery solution and in addition the comparative cheapness of alepol, it is the drug of choice in countries which have to import anti-leprosy drugs. The chief drawback to the use of alepol is the pain and reaction that sometimes occur. This is due to the precipitation of the fatty acids which is likely to occur if alepol is kept for a long time or is brought into contact with concentrated acids like carbolic acid. If alepol solution is carefully prepared and if the spirit used in the sterilisation of the needles of the syringe is completely dried out, this precipitation factor and consequently the pain may be minimised to a great extent.

Ethyl esters of chaulmoogra oil. The ethyl esters of the fatty acids are liquid preparations made more fluid than the original oil and are suitable for intra-muscular injections.

Two methods are usually followed—the hot process or the rapid method, and the cold process or the slow method.

Hot process. The original method required the help of a chemist and a chemical laboratory, as it necessitated the distillation of the esters at much reduced pressure. A simpler method is as follows: 425 gm. of crude cold-drawn hydnocarpus oil, 552 c.cm. of 96 per cent. ethyl alcohol and 31.87 c.cm. of sulphuric acid (sp. gr. 1.845) are placed in a 2½ litre flask fitted with a reflux condenser; the alcohol and oil are mixed before the acid is added. The contents are allowed to boil on a water-bath for 24 hours without intermission. The reaction product is then transferred to a separating funnel and washed with water and then with 1.0 per cent. caustic soda solution; crystals of sodium chloride are then added gradually when the emulsion breaks up and esters rise to the surface. Distillation is not considered necessary now-a-days. According to Muir if the mixture is used without distillation it is less painful.

The cold process. This is a lengthy process but can be carried out in any leper institution with the most simple apparatus. The simple cold process of Muir is as follows. The oil, alcohol and acid are mixed in the proportion of 425 gm. of crude cold drawn hydnocarpus oil, 552 c.cm. of 96 per cent. ethyl alcohol and 31.87 c.cm. of sulphuric acid (sp. gr. 1.845), in a 4 lb. bottle with a tightly fitting glass stopper and left until the process of esterisation is completed, the bottle being shaken once or twice a day to mix the layers and kept in a warm place, as in the sun, to hasten the process. As it proceeds the esters rise to the top, after which occurrence half the time taken for them to rise should be allowed to elapse, when the lower layer is drawn off, and the remaining upper layer of esters washed twice with an equal volume of water and then with a 1.0 per cent. solution of caustic soda. The esters may be put up in glass-stoppered bottles or in ampoules and sterilised at 120°C for half an hour or on a water-bath at 100°C on three successive days. Antiseptics may also be added, Muir preferring 4 per cent. creosote which in Culsion treatment-tests were found to increase the value of the preparation. In the Philippines 0.5 per cent. of iodine is added by a special method which lessens the irritant properties.

These were first used on a large scale in Hawaii by Dean and McDonald (1919). In India, Ghosh (1920) independently of Dean, prepared the ethyl esters and suggested their use to Rogers. The injection of the esters of the pure acid, however,

proved somewhat irritating to the tissues of the body and Rogers discontinued its use after some time. Later, McDonald used the ethyl esters with 2 per cent. iodine by weight, with good results. Rodriguez (1925) stated that the iodized ethyl esters proved to be very efficacious and 77.3 per cent. of cases improved. This treatment soon became very popular in leper institutions. It has been used very extensively at Cullion by Lara (1930) and in Calcutta by Muir and in nearly every other active centre of leprosy treatment.

The dosage recommended in the Philippines is 2 to 5 c.cm. once a week intramuscularly. Muir mixed an equal quantity of the esters and olive oil to lessen the pain. His formula was known as the E. C. C. O. mixture and was used extensively throughout India and in the Malay peninsula at one time. It consisted of ethyl ester of fatty acids of *H. Wightiana* 1 c.cm., camphor 1 gm., creosote 1 c.cm., olive oil 2.5 c.cm. Muir used 1 c.cm. of this mixture to start with, increasing by 0.5 c.cm. at each dose twice a week up to a maximum of 10 c.cm. He injected any dose up to 4 c.cm. subcutaneously beneath the skin lesions ('plancha method'—to be described later) and any excess into the gluteal muscle. He also tried it intravenously but gave it up as less effective and less safe.

The standard preparation originally used by McDonald and Dean contained 2 per cent. iodine, but Muir showed that iodine in the mixture yields no advantage whatsoever. The addition of creosote was shown by Samson to be useful and the clinical trials are stated to yield more favourable results. The preparation known as 'Heiser's mixture' contained camphorated oil, resorcin and ether. The camphor was not reported on favourably by some but still is being used. It has been used to a considerable extent in China by Fowler (1922), Wilson (1924), Read and Feng (1925) and in many other active centres of leprosy treatment. A number of preparations of ethyl esters is available in the market, the best known of these being 'moogrol' (British), 'antileprol' (German), 'antilebrine' (Italian).

The ethyl esters, though effective are not very well tolerated especially in skin cases where they are liable to produce

reactions which are not conducive to the well being of the patient. For this reason, this remedy is now being largely replaced by the pure oil or one of the salts of hydnocarpic acid which are less active in this direction. Moreover, as the sodium salts such as alepol are now much less irritating than they formerly were, the advantages of exporting a powder compared with a fluid are so great that the esters have been largely replaced.

The intradermal or the 'plancha' method. Until recently, chaulmoogra oil and esters were most commonly injected intramuscularly, subcutaneous infiltration under the lesions (Rogers and Muir 1925) being an alternative method. The sodium salts are given intravenously as well as intramuscularly and subcutaneously. The intradermal method, formerly used occasionally by some workers, Rogers (1917), McDonald and Dean (1920), and Muir et al (1923), was first used extensively by Lara, Nicolas, Velasco et al (1929) in the Philippines who called it the *plancha* or infiltration method. The esters are injected by them into the actual lesions in the skin by means of multiple small punctures raising a wheal not more than one centimetre in diameter. Lara and Nicholas report on five early cases and one slightly more advanced case found among the children born at Culion. Four of them became negative bacteriologically in one to two months and one in 5 months, the quickest results they know of in the literature. Nolasco (1929) found on histological examination that the remaining pathological material in infiltrated lesions was only one-half to one-fourth of that found in uninfiltrated ones. The superiority of this method is easily proved, as shown by Muir (1931). He chose patients with marked symmetrical lesions and infiltrated those on the one side of the body, leaving those on the other side as controls. Improvement was much more marked on the infiltrated side. A modified method of giving intradermal injections is described by Muir (1932). A short guarded needle is used to prevent its penetrating too far into the tissues. The actual amount of penetration is regulated, according to the thickness of the skin, by the angle at which the needle is introduced. One-half to one drop is injected at each puncture, and up to 5 c.cm. may be

injected at a sitting. The plancha method of the Philippine workers, including the infiltration of subcutaneous leproma, undoubtedly gives better results than intramuscular and subcutaneous injections, and should be adopted as far as possible.

Relative value of chaulmoogra oil and esters. The esters of chaulmoogra oil were originally made with a view to having a preparation less irritating and more easily absorbed than the oil itself. But the manufacture of oil from ripe, fresh seeds has resulted in a product which causes very little irritation, and the adoption of the intradermal method has to a certain extent done away with the need for quick absorption. The oil when injected by this method, remains longer than the esters in the infiltrated lesions, and may thus by its local action continue to produce beneficial results for a longer period. In patients with extensive lesions it may take several months before the whole affected area of the skin can be infiltrated. By intradermal injection of the oil a mild therapeutic effect can be obtained which continues for a period of several weeks in the infiltrated areas. The *H. Wightiana* oil obtainable in India, with 4 per cent. creosote added, causes on the whole no more irritation than the creosoted esters. In the Philippines it is found necessary to iodize esters in order to reduce their irritating qualities. In Calcutta, on the other hand, the esters without iodine were found less irritating than esters iodised by the method used in the Culsion Colony. This may be due to a purer form of the oil being available in Calcutta or to the method of preparation.

One disadvantage of the oil, as compared with the esters in intradermal infiltration, is that the former, being more viscous, does not penetrate the intercellular spaces as readily as the latter. This is overcome by heating the creosoted oil on a water bath to a temperature of 55°C. before drawing it into the syringe. Not more than one drop (0.06 c.cm.) should be injected at each puncture. Thus to inject 6 c.cm., which may usually be regarded as the maximum dose at a sitting, some 80 to 100 punctures should be made.

In India, the number of patients that can be treated is governed to a great extent by the expense. Recently, the

Medical Stores Dépôt, Madras, have manufactured Hydnocarpus Esters with creosote and sell at the cost price of Re. 1-3-0, a lb., to leprosy clinics. This is cheaper than the pure oil with creosote. It is easier to ensure a uniformly low standard of irritation with the esters, especially in rural dispensaries. The quality of the esters, the manufacture of which is a highly technical process, is apt to vary with the skill and experience of the makers, and a series of painful injections may frighten away patients. Where uniformly painless oil is available this is much less likely to occur. For the injection of oil a needle of a slightly larger bore is necessary. There is a great advantage with the short, guarded needles, now widely used in India (Muir 1932) as the oil passes more easily and multiple punctures can be made much more rapidly than with long needles. The relative efficacy of intradermal injection of oil and esters has not yet been fully tested, but experience up to date has shown that both are effective, and that if either of them is better than the other the difference is not great.

OTHER OILS USED IN LEPROSY

Oils with unsaturated fatty acids. In accordance with the theory mentioned in the last section, it is the unsaturated fatty acids of chaulmoogra oil (iodine value 90.7 to 104) which form the chief therapeutic factor. Various other oils of high iodine value have been tried, chief among these are cod-liver oil (iodine value 154 to 181), linseed oil (iodine value 173 to 201), soya bean oil (iodine value 137 to 143).

Rogers (1921) mentioned that all lesions had disappeared in 5 out of 20 cases treated with sodium morrhuate (prepared from cod-liver oil), as compared with similar results in 9 out of 15 patients treated with chaulmoogra preparations. This tended to show that the value of cod-liver oil preparations though considerable is not equal to that of chaulmoogra oil.

Eucalyptol. Amaral and Paranhos (1908) injected a hundred per cent. oily solution intramuscularly thrice a week. It was apt to cause diarrhoea, but satisfactory results were obtained in 70 patients, the disease being arrested and signs of intoxication diminished.

Gurjun oil. Hansen and Looft (1895) mention the use of this oil given orally in lime water without effect.

Calophyllum bigator. Neff (1929) reports good results with the injection of esters prepared from the oil of this tree, especially in relieving the nerve pain often present in lepra reaction.

HEAVY METALS

Antimony. Cawston (1920) reported decided improvement in patients with the use of a 2 per cent. solution of tartar emetic given intravenously; especially in the healing up of ulcers and absence of recurrence. Maples (1921) reported good results with tartar emetic but declared that in doses consistent with safety it does not cure. Trueherz (1927) alternated intravenous injections of tartar emetic, 2 to 3 c.cm. of a 2 per cent. solution every 4th day, with intravenous injections of antileprol, a thin preparation^o of chaulmoogra oil. Hoffmann (1927) found antimony a useful drug in combination with chaulmoogra preparations, the two attacking the disease from different sides. He used von Heyden stibenyl, antimosan and stibosan intravenously. Muir (1927, 1930) advised intravenous injection of tartar emetic in doses of 0.02 to 0.04 mg. thrice a week for reducing the lepra reaction caused by iodides and in other ways.

A perusal of the above literature appears to show that antimony compounds have the power of controlling the condition known as the 'lepra reaction.'

Copper. Sugai (1916) used copper cyanide with apparent disappearance of symptoms after 6 to 12 months' treatment. Takano (1916) used cyanocuprol, 20 to 24 mgm. once a week intravenously. He stated that, unless given slowly with the patient lying down, anaphylactic symptoms may result after the 5th or a later dose. Henderson (1928) reported trials with another preparation containing 14.3 per cent. of copper. It lessened nerve pain but had little beneficial effect on the disease.

Mercury. Hansen and Looft (1895) report internal and external use of mercury resulting in patients becoming worse.

Mercurochrome. Denny (1925) injected 5 mgm. per kilo. intravenously (34 c.cm. of a 1 per cent. solution in patients of 150 lb. in 44 cases). As severe reactions followed, this had to be reduced to half the dose. Rao and Roy (1932) giving smaller doses than the above (10 c.cm. of a 1 per cent. solution) in 12 reacting cases, obtained cessation of reaction. Muir and Chatterji (1932) beginning with 3 c.cm. of a 1 per cent. solution and increasing to 10 c.cm., injections being given intravenously once a week, found that septic conditions of the skin, gums and the gastro-intestinal tract were cleared up and consequently the lepra reaction could be controlled. They, however, emphasise the danger of continued use of mercurochrome as the necrosis and liquefaction produced in the leproma tend to continue for many months and the consequent lowering of the patient's resistance cannot be controlled. As soon as the septic condition or the lepra reaction has yielded, the use of this drug should be discontinued.

Avenyl is a mercury preparation soluble (0.25 to 0.5 per cent.) in chaulmoogra oil and esters. (For further details see page 753).

Gold. Puente and Pierini (1926) used sanocrysin in doses of 0.025 to 0.5 gm. in 5 patients with slight improvement in some cases associated with diarrhoea, rise of temperature and weakness. Hoffmann (1927) obtained resolution in eye conditions with Krysolgan. Paldrock (1927, 1928, 1929 and 1930) used solganal, in combination with CO₂ snow applied to the nodules. The number of patients treated was small, 6 or 7, but Paldrock claims that his treatment is the only one which gives specific results. He also used lopion, another gold preparation, which causes loss of weight and gastro-intestinal derangement. Feldt (1928) considered that such preparations as durocantha, gold potassium cyanate, krysolgan and solganal act by stimulating the natural defensive processes of the body through the reticulo-endothelial system and thus excite the natural healing powers. Muir (1932) tried solganal in a series of cases, but found that it produced unfavourable reactions. The question of the advisability of reaction production is still unsettled, and the superiority of gold preparations over other cheaper forms of treatment would have to be well established before it could be brought into general use. The great majority of leprosy patients are very poor, while this form of treatment is necessarily very expensive.

Lead. Sandes (1913) tried the lead salts without improvement. Lead selenide injections have been tried by the Calcutta workers without benefit.

Bismuth was used by Matta (1923) in the form of trepol. No improvement was recorded.

Arsenic. Hopkins (1916) found that Fowler's solution diminished the duration and severity of lepra fever. Brault (1907) considered atoxyl more useful in leprosy than all other forms of arsenic then available. On the whole arsenic has not been found to produce any permanent good results excepting in cases complicated with syphilis.

Summary of the action of heavy metals in leprosy. Most of the heavy metals appear to have a double action. In large doses they can produce a lepra reaction, with beneficial effects in some cases, if carefully regulated and not pressed too much. In small doses they have the property of controlling or limiting lepra reaction.

MISCELLANEOUS REMEDIES

In addition to the above remedies there are a considerable number of drugs which is difficult to enumerate. Only a few of the important ones will be mentioned here.

Carbolic acid was used by Hansen (1895) in 53 cases. It produced no effect in the disease.

Sodium salicylate was considered by Danielssen (1895) as a good tonic in leprosy; 0.25 gm., dissolved in 2 c.cm. of normal saline and

injected intravenously, relieves the bone and joint pains common in leprosy.

Creosote was given orally by Hansen and Looft (1895) without effect. Muir (1925) injected it in combination with hydnocarpus esters, adding also camphor. Later (1923) he began to use it along with hydnocarpus oil and esters in a 4 per cent. solution. It decreases the viscosity of the oil, and is antifebrile, antiseptic and tonic. Samson (1923) after a well-controlled experiment with four groups obtained the best results with the cases injected with creosote dissolved in chaulmoogra esters. He found that it stimulates the appetite and causes an increase in weight.

Fibrolysin was also tried by the same worker (1928) and also by Figueredo (1929) with negative results.

Aniline dyes such as methylene blue, trypan blue, carbol fuchsin, etc., have recently been used in the treatment of leprosy by various workers. Some workers claim promising results, but it is still too soon to make any definite pronouncement.

External or local treatment. Leprosy is a systemic disease and any form of local treatment is not expected to help the condition. Local treatment, however, sometimes becomes necessary to remove the unsightly leprous nodules and speed up the absorption of the leproma. Caustics and local counter-irritants in the form of carbon dioxide snow and repeated freezing with ethyl chloride have been used from time to time. Trichloroacetic acid applications have also been employed.

Hot mineral baths have been recommended. These apparently have no useful action on the disease itself but are of benefit indirectly by improving the general nutrition of the patient.

Radio-therapy and electro-therapy. Several workers have reported beneficial results with X-rays, radium, ultra-violet rays, diathermy, etc. These methods apparently have no direct effect on the disease but are known to relieve the neuralgias and the paræsthesias so common in leprosy. With regard to the ultra-violet rays, Denney (1928) found that ultra-violet rays relieved pains and healed up perforating ulcers. Rose (1928) found ultra-violet rays combined with zinc ionization of great value in healing up perforating ulcers of many years standing. Muir (1930) found that ultra-violet rays improved the general resistance of patients to leprosy, lowered the sedimentation rate and are useful in clearing up complicating tinea and streptococcal infections which are very frequently associated with leprosy.

Irradiation of chaulmoogra oil. Hirst (1925) suggested that the effect of the chaulmoogra oil might be increased by irradiation of the oil with certain forms of sun or light rays. Labernadie (1929) irradiated *H. wightiana* oil by means of a mercury quartz lamp and added ergosterol to another sample. The number of cases treated however is too small to warrant any definite conclusions on the utility of the method.

Vaccines and serum inoculation. The discovery of the lepra bacillus and the success obtained in producing immunity in other diseases by the injection of vaccines and sera, led to various attempts at immunity production by injections of bacillary suspensions, sera, etc.

Autogenous vaccines have been used by many workers. Wooby (1907) used graded doses of lepra bacilli obtained from ground-up nodules and killed by heat. Nicholls (1908) placed a subcutaneous nodule in broth and after incubating for 14 days, dessicated the whole and powdered it in an agate mortar. A suspension was made from this and injected. Walker (1924) used a standardised suspension prepared by grinding up nodules with sand and reported promising results in the cases treated. Wayson (1921) produced bullæ by means of CO₂ snow applied over the lesions; the fluid obtained was reinjected after adding iodine. Hansen (1926) obtained bacilli in the same way from the blister fluid of lepers and injected them after incubating for 2 to 3 months. Collens (1930) prepared a bacillary suspension by triturating leprous nodules with 60 per cent. alcohol and glycerine in equal parts. This treatment was used in combination with injections of chaulmoogra esters and very good results were reported.

Vaccine treatment in leprosy is not possible if a large number of patients has to be treated for prolonged periods. Active suspensions of the leprosy bacillus can only be obtained in advanced leprosy cases with nodules all over the body and this is not always possible.

Tubercle bacilli and their products. Both the organisms of leprosy and tuberculosis are similar in that both of them have an acid-fast coating. The reputation of tuberculin as a useful agent in the treatment of tuberculosis led to the use of

this substance in leprosy. Its use however did not give satisfactory results in the hands of Danielssen (1891) ; Goldschmidt (1891) and Arnand (1896) however obtained improvement in several cases. Lie (1905) considered that the smallest doses gave the best results and that tuberculin deserved further trial. Row (1926) used suspensions of autolysed cultures of tubercle bacilli washed free from fatty substances in petrol ether. He reported favourable results by this method. The consensus of opinion at present is that tuberculins or the bacillary emulsions are not very useful.

Suspensions of acid-fast organisms. Apart from *B. tuberculosis* and its products, various acid-fast organisms and their products or extracts have been inoculated by various workers with the idea of producing a specific active immunity. Deycke and Raschid (1908) popularised a preparation (Nastin) which consisted of a killed suspension of an acid-fast organism obtained from leprous nodules. Later, they mixed this suspension with benzyl chloride, and called it 'Nastin-B'. Many workers appear to have obtained favourable results with this preparation in the earlier years. Later observations under more controlled and careful supervision showed that though some initial benefits might result, no permanent improvement was discernible.

Rost's 'leprolin' also enjoyed a temporary phase of popularity only to be cried down later.

Markianos (1930) digested rat-leprosy bacilli with pepsin and pancreatin, washed them with water and then with alcohol and then defatted. Suspensions of these organisms were injected in increasing doses into patients. Some improvements in patients thus treated were claimed by the worker.

Sera. Various attempts have been made to produce an immune sera by injection of material taken from leprous subjects or supposed cultures of lepra bacilli into horses. Results were not encouraging. Leverde (1897) inoculated sheep and goats with the juice of nodules and treated many patients with the serum without any benefit.

Autohaemotherapy. Sezaryl (1930) inoculated seven cases of leprosy subcutaneously and intravenously with their own

blood, 5 to 10 c.cm. being given at a time. Subjective symptoms and nerve pains were reported to have been diminished.

Protein shock. Muir (1923) used a suspension of Kedrowsky's acid-fast bacillus intravenously and obtained favourable results due to the protein shock induced. Manson-Bahr (1928) gave typhoid-paratyphoid vaccine intravenously and thought that the improvement which resulted was due to the protein shock. Mixed streptococcal and staphylococcal vaccine, milk injections, etc., have also been tried. There is no doubt that the general condition of the patient is frequently very much improved by such injections. It is likely that the beneficial effects so often observed with various vaccines, sera and bacillary emulsions are due to the shock-like reaction produced by the foreign protein contained in them.

General health and leprosy. The general health of the patient has a marked influence on the course of the disease. Many leprologists have more than once emphasized the importance of the subject. Lebœuf (1914) laid stress on rest, good hygiene and good food as in tuberculosis. Muir et al (1923) considered all measures calculated to strengthen the body resistance of the patient, of supreme importance in the treatment. Wade and Rodriguez (1927) stated that exposure, improper feeding, weakening diseases and sexual over-activity were all contributory factors in lowering the resistance of the patient and in helping the rapid progress of the disease. Wilson (1929) showed the marked influence on the progress of the disease that can be produced by exercise and cheerful mental and physical occupation in his leper colony in Korea. In the Leonard Wood Memorial International Leprosy Conference held in the Philippines in 1931, experienced physicians agreed that careful and persistent efforts to eliminate intercurrent affections which tend to reduce the general resistance of the patient are essential to successful therapy. General measures, like personal hygiene, supervised or graduated physical exercise, occupational therapy, the stimulation of moral and mental welfare, are also of definite value. Diet demands the primary consideration.

Diet. Embrey (1923) carried out a large diet experiment in the Culion Leper Colony, and found that, by balancing the diet the general health of the patients improved and progress under special treatment was enhanced. The importance of diet in the causation of leprosy, and consequently in its treatment, is brought out by the extensive survey carried out by Santra (1927), which shows the bearing of famine, ill-balanced diet and badly preserved or decomposing food on the incidence of leprosy. Rodriguez (1925) states that the importance of proper diet and sufficient exercise cannot be exaggerated in the treatment of leprosy, and general tonics are of value.

The rôle of intercurrent diseases. It has already been mentioned that intercurrent diseases favour the progress of the disease by lowering the general resistance. A review of the literature however shows that in many instances complicating diseases seem to have actually benefited the condition. Thus, Denney (1922) referred to the effect of vaccination on 118 leprosy patients; there were febrile reactions in 51 out of 91 nodular cases, but they appeared to improve after the reactions passed off. Muir (1927) referred to several cases in which kala-azar complicated fairly advanced leprosy. The patients later recovered from the complicating disease under treatment and the improvement in the leprosy complicated by the kala-azar was so striking that other leprosy patients volunteered to have themselves infected with kala-azar. Pinard (1929) mentioned temporary amelioration of leprosy following an artificial infection with benign tertian malaria. Bahnia (1930) mentioned the effects of a severe attack of pneumonia; the leprosy patches cleared up so rapidly thereafter that he believed the acute febrile condition was responsible for the improvement. This beneficial effect of intercurrent diseases is therefore difficult to explain. The improvement induced in these ways is always temporary. Muir, after testing the method by inducing such diseases as malaria, kala-azar and rat-bite fever, concluded that, though the signs of leprosy may be diminished safely to a certain extent, final recovery is not possible and ultimately the disease is never improved, but always retarded, due to complicating factors.

Lepra reaction. Lepra reaction is one of the most commonly known phenomena in leprosy. In discussing the treatment of leprosy, we cannot leave aside its important relationship to the disease. The clinical signs of lepra reaction are swelling up of formerly apparent lesions, the appearance of lesions in parts where they were not formerly visible and a general febrile condition. Bacillæmia is present, at least when reaction occurs in the more advanced skin cases. In nerve leprosy, the involved nerves become swollen and painful. The lepra reaction may occur apparently spontaneously, but it is generally associated with lowering of the general health due to some accompanying disease or other causes.

Lepra reaction and leprosy treatment. Some authors are of opinion that the lepra reaction is beneficial in leprosy, while others hold that the reaction is distinctly harmful. It is very difficult to give a definite opinion on its real value as distinguished leprologists have stated entirely opposite views. Rogers (1916) writing of treatment with gynocardate of soda stated that the most striking result is the occurrence of definite local reactions in the diseased tissues, sometimes accompanied by fever. This reaction is beneficial to the patient by causing absorption of the leprous nodules. Hollmann and Dean (1919) mentioned that, with fractional esters, in all nodular cases there were local reactions at the site of leprous lesions. Denney (1922) wrote that after vaccination febrile attacks occurred, followed by improvement. McDonald (1921), on the other hand, said that reactions are manifestations of toxæmia and usually retard the progress of the disease. Rodriguez (1925) expressed an almost similar opinion, while Lara (1928) was more definite and stated that improvement was greater in cases not showing reaction and that reactions were definitely dangerous. The position therefore appears to indicate that mild reactions in healthy patients are usually attended with beneficial results but severe reactions in undernourished patients with consequent low general resistance are injurious to the disease.

For purposes of treatment lepra reaction may conveniently be divided into two types: (a) Reactions of a toxic nature which subside when the cause disappears automatically or is removed

by the treatment. (b) Reactions in which in addition to the presence of toxæmia, a sensitization factor is present. In this latter type, the reactions tend to recur at frequent intervals or may continue indefinitely. The treatment must vary according to the type. In the former type the treatment consists in removing the cause, if necessary. Thus a single dose of potassium iodide will cause a reaction which subsides in an unsensitized patient with the excretion of the drug from the body. An attack of malaria may cause a reaction which subsides after a few days of quinine administration.

In the latter type a vicious circle is formed, the depression of health caused by the reaction being sufficient to prevent its subsiding. Such a condition may continue for weeks or months, and unless effective treatment is adopted, recurs frequently, sometimes at regular fortnightly intervals. It is necessary, therefore, in addition to removing the cause, to take special means to desensitise the patient.

The fact that excessive treatment may result in the production of a lepra reaction of the second type is well-known to leprologists. The common method adopted to obviate this has been to push special drugs until signs of reaction begin to appear and then to stop treatment till the patient recovers, after which the special treatment is resumed. Ehlers (1900) and Crocker (1900) recommended intermittent courses of mercury. Heiser (1914) gave intermittent courses of chaulmoogra and resorcin. Paldrock (1928) allowed his patients a six months' interval to recover after a course of CO₂ snow and solganal before resuming the treatment.

The following references from the literature mention certain drugs which have been used for the treatment of lepra reaction.

Fowler's solution was found by Hopkins (1916) to be the best remedy for diminishing the duration and severity of lepra fever.

Alkalis have been used by many workers both orally and intravenously. Rodriguez (1925) mentions giving intravenously 20 to 25 c.cm. of a saturated solution of sodium bicarbonate daily for several days. He gave 2 to 3 gm. of sodium bicarbonate

orally 4 or 5 times a day. Roy (1931) recorded two cases of severe and intractable pain in nerve leprosy unalleviated by various other drugs, which yielded to two intravenous injections of 150 and 200 c.cm. respectively of 0.5 per cent. sodium bicarbonate in normal saline with 5 days interval. On the other hand, the patient may become worse after 20 c.cm. of the same solution.

Calcium chloride was given, as advised by Mitsuda, by Rodriguez (1925) in a 2 per cent. solution intravenously in doses of 20 to 30 c.cm. daily for a week. Hasle (1929) gave intravenous injections of 10 c.cm. of freshly prepared 2 per cent. pure calcium chloride, 15 injections in one month, and a second series after an interval of 15 days, without any ill effects; in 15 of the 20 cases treated there was healing of ulcers, softening of nodules, relief of neuralgic pains and benefit to the general health.

Adrenalin was recommended by Muir (Rogers and Muir 1925) for the relief of nerve reaction, 3 min. being given in saline solution infiltrated subcutaneously along the course of the nerve; this often gives relief within a few minutes. He also stated (1924) that two min. of 1 in 1,000 adrenalin solution mixed with 30 min. of saline and injected daily intramuscularly is often useful in stopping leprotic fever. Wheatley (1926) used this remedy in the general lepra reaction with good results. Green (1929) used adrenalin to desensitise patients. Eubanas (1931) used 1.0 to 1.5 c.cm. of a mixture containing $\frac{1}{2}$ to 1 per cent. cocaine and 5 per cent. adrenalin solution in nerve reactions. He usually obtained relief of pain after an average of 2 injections and no recurrence took place within six months.

Ephedrine sulphate was used by Muir and Chatterjee (1928) in place of adrenalin in nerve reaction. This drug has the advantage of being effective when given by the mouth in 0.02 gm. doses. Relief is often obtained within half to one hour. It may also be given in the same dose suspended in 10 c.cm. of a $\frac{1}{2}$ per cent. sodium bicarbonate solution infiltrated along the course of the painful nerve, often with almost instantaneous relief. Muir found however that in a certain proportion of cases

neither adrenalin nor ephedrine has any effect in stopping nerve reaction.

Potassium antimony tartrate is one of the most useful drugs in the control of the lepra reaction.

Mercurochrome is also valuable, especially when reaction is caused by complicating septic infection.

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CHAPTER VI

TUBERCULOSIS

Tuberculosis is an infection caused by *Mycobacterium tuberculosis*. The lesions are characterised by nodular bodies, tubercles and diffuse infiltrations which either undergo caseation, necrosis and ulceration or heal with sclerosis and calcification. It is responsible for one-seventh of all deaths in the world. It has been described as the commonest, most fatal, and perhaps the saddest of those diseases which oppress mankind. It spares neither age, sex, race nor nationality. It is wide-spread amongst civilised communities. In primitive peoples living in their native countries tuberculosis either does not occur or is very uncommon. The incidence of the disease increases proportionately to the degree of crowding, as is especially common in capitals and great commercial and manufacturing towns. Tuberculosis in the human subjects takes many forms ; it may be localised or more or less disseminated. In children and susceptible individuals acute generalised forms predominate, while in resistant individuals it is localised. No part of the body is immune, but such organs as the lungs in adults and bronchial glands in children have a predilection for tuberculous infection. The common conception of tuberculous infection is that it generally occurs during the early years of childhood. Pulmonary tuberculosis in the adult shows the characteristics of localisation and chronicity because it occurs in a person immunised by a mild infection in his early years. Heimbeck (1931) studied the incidence of tuberculous infection and its relation to morbidity at various ages and in various classes. He used von Pirquet's cutaneous tuberculin test and his conclusions were that in childhood only a small number is infected with tuberculosis, and the percentage increases slowly during this period of life as the children are kept at home, due to contact with cases of tuberculosis. During working life the second and great period of infection begins. It is during youth that the majority of people and all who have escaped infection

during childhood become infected. There is comparatively less morbidity during childhood and a wide-spread morbidity during the young adult period, corresponding to the time when the second period of infection occurs.

The problem of tuberculous infection in India is somewhat different from that of Europe or other countries. The infection rate in India is considerably lower than that of European countries, and this is due to the fact that the urban population in this country is 7 to 20 per cent. of the total population as compared to 80 per cent. in England and Wales, 56.2 per cent. in U.S.A. and 53.7 per cent. in Canada. India stands intermediate in position between the highly bacillized European races and the scarcely bacillized African races. The incidence of the disease varies greatly in rural and urban areas, between small and large cities, in different industrial areas, and also between various industries. Though tubercle bacilli are the essential cause of tuberculosis such factors as living conditions, nutrition, habits and customs of the people ultimately determine the susceptibility or resistance to infection. Thus in India the less immune people such as the Bhils and Gurkhas are very liable to infection when they migrate to large cities.

The following figures of the incidence of tuberculous infection in different ages among people in India as based on positive von Pirquet test will be interesting (Ukil, 1934).

Age	Incidence	Age	Incidence
0 to 5	... 11.4	21 to 25	... 50
6 to 10	... 30.1	26 to 30	... 52.7
11 to 15	... 33.3	31 to 40	... 56
16 to 20	... 38.1	41 to 50	... 59.4

Tuberculosis in human beings was previously believed to be a hereditary malady, but careful autopsies on the foetus and infection experiments with their tissues have failed to demonstrate the existence of tubercle bacilli in their organs, and it is admitted that the hereditary transmission of tuberculosis is of minor importance. The offspring of the tuberculous patients if separated immediately from their parents and guarded

STATISTICS OF DEATHS FROM TUBERCLE OF THE LUNG AS COMPARED WITH TOTAL DEATHS, IN 1932,
IN VARIOUS PROVINCES OF INDIA

Provinces.	Total deaths.	Deaths from Tubercle of the lungs.	Percentage of deaths from tubercle of the lungs to total deaths.	Respiratory death rate per 1000.	Sanatoria.
Bengal ...	1,022,219	1,180	1'1	1'2	1
Bihar & Orissa ...	757,470	0'1	1
Bombay ...	502,474	21,070	4'2	4'2	6
Burma (towns) ...	40,644	2,104	5'2	1'0	Nil
Central Provinces ...	416,977	1,631	0'4	2'0	1
Delhi ...	15,737	593	3'8	6'2	Nil
Madras ...	839,265	2'0	2
Punjab ...	509,740	2'5	1
United Provinces -	1,076,225	5,791	0'5	0'7	2

against subsequent infection generally remain perfectly free from the disease. Recently, a filterable form of tubercle bacillus has been demonstrated in the placental tissue but the evidence with regard to it is not conclusive.

The organism. *Mycobacterium tuberculosis* is a minute rod-shaped organism slightly bent or curved with an average length of 3 to 4 μ . When stained it may present a beaded appearance. Aberrant forms are not uncommon, viz. long filaments or branched forms.

Tubercle bacilli may be divided by cultural and pathogenicity reactions into four types—human, bovine, avian and cold-blooded. Of these the first two only are found in natural infections of man. The frequency of the bovine and human types in different varieties of tuberculosis in patients of different ages has been worked out. It is clear that, taking all ages into consideration, the majority of infections are due to the human type. The proportion of bovine infections is highest during the first 5 years of life, and in adults, infections due to the bovine bacillus are uncommon. Pulmonary tuberculosis is almost invariably due to the human type. Primary abdominal tuberculosis is almost invariably due to the bovine type, but secondary abdominal tuberculosis which occurs most frequently as a late complication in pulmonary tuberculosis is generally due to the human type. The surgical types of tuberculosis, involving bones, joints, lymph nodes, etc., are usually caused by the bovine bacillus. It is interesting to note that pulmonary tuberculosis and surgical types are seldom found together.

Mode of infection. The majority of the cases of tuberculosis in adults and children may be attributed to infection after birth. Tubercle bacilli may enter the body through all surfaces, e.g., the skin; conjunctivæ and the lining membranes of the genito-urinary, alimentary and respiratory passages. The respiratory tract is the most frequent avenue of infection.

The picture of tuberculosis varies with the age, the susceptibility, dose and the mode of infection. It is characterised by enlargement of the lymphatic glands in children with a tendency to generalisation. Enlargement of the tracheo-bronchial lymph glands with or without involvement of the lungs is of common occurrence; most authorities believe that this is almost always secondary to a focus in the lungs. The other commonly encountered variety is that in which the mesenteric glands show tuberculous lesions which may or may not be accompanied by ulceration of the intestine. In young children tuberculous infection frequently terminates in death from generalised military tuberculosis or tuberculous meningitis. In older children who have greater powers of resistance, the lesions generally become chronic with localization in the bones, joints, skin, kidney or testes. In adults, the lungs are more frequently involved and the process extends by direct propagation with the lung and along continuous mucous surfaces.

Natural tuberculosis is a local disease in the beginning; if the person is susceptible, a tuberculous lesion develops at the site of lodgement of the bacilli. If the primary focus starts in the lungs either in a bronchiole, an infundibulum or an alveolus, a typical lesion develops with caseation and necrosis. If the focus is in a lymphoid follicle in the intestine, the nodule becomes necrotic, and caseous in the centre; it then softens and ulcerates. From the initial focus of infection the disease spreads by way of the lymphatic stream, circulation or along continuous surfaces. The lymphatic mode of spread occurs commonly in children. The bacilli lodge in the lymph glands where they form characteristic tuberculous lesions, or chains of tubercles may develop in the lymphatic vessels of the mesentery, in the lungs, in the peribronchial tissues and in other places as well. Infection passes from one set of glands to other groups or directly into the thoracic duct. When bacilli in large numbers gain entrance into the blood stream, acute miliary or chronic disseminated tuberculosis develops. The blood stream may also be invaded by an eruption into a vein or artery from a tubercle which has ulcerated into the wall of the vessel. If the number of invading bacilli is small, chronic forms of tuberculosis affecting mainly the bones, joints or kidneys result. Direct extension of tuberculous process is not infrequent. Broncho-pneumonia may result from the breaking down of a caseous gland into a bronchus; the pleura and the pericardium may be infected from a focus in the lung; tuberculosis of the kidney may lead to descending infection of the ureters and the bladder.

The mode of infection of the lungs has not been finally settled. Koch in 1884 and numerous other investigators found that the avenue of infection in pulmonary tuberculosis was the respiratory path. Calmette asserts that it is by way of the alimentary canal that the lungs are infected; he found that very much smaller doses of the bacilli are needed to produce the disease by this route than by inhalation. Most workers, however, maintain that inhalation is the principal source of pulmonary infection. Aschoff argues that in the guinea-pig, inhalation of from 5 to 20 bacilli is sufficient for the purpose, but that feeding with 20,000 bacilli may fail. According to other workers, the infection occurs chiefly through the tonsils with or without local lesions. The bacilli pass into the cervical lymph nodes, travel down this chain to the apical pleura or to glands at the root of the lung and thence into the lung substance. Though it has been shown that tubercle bacilli may pass through intact pharyngeal and intestinal mucous membrane and thus infect other organs, this mode of origin of pulmonary tuberculosis is extremely infrequent.

Clinical Varieties of Tuberculosis

(a) *Tuberculosis of the lymphatic system.* Tuberculosis of the lymph nodes is met with at all ages, but is more common in children than in adults, and may occur in old age. It may occur in the form of generalised tuberculous lymphadenitis or local tuberculous adenitis. In exceptional

instances a diffuse tuberculosis of nearly all the lymph glands of the body is met with. In infants and children there is a form of general tuberculous adenitis in which the various groups of glands are successively, more rarely simultaneously, involved and in which death is caused either by cachexia or by an acute miliary process. Glands of the neck which drain the lymph from the mouth, throat, nose, ears, and scalp are more commonly involved. Some local focus of irritation is usually present in the form of pediculi capitis, decayed teeth, chronic otorrhœa, adenoids or eczema of the face. The localised form of cervical adenitis is most common in children particularly in those whose surroundings are unhealthy and whose general conditions are deteriorated by insufficient or bad food and want of fresh air. The progress of this form of adenitis is slow and tedious; death rarely follows. The tracheo-bronchial lymph glands are almost invariably involved in cases of initial infection in tuberculosis. In children the bronchial adenitis is apt to be associated with suppuration. When the glands attain some size they give rise to various symptoms by pressing on the adjoining mediastinal structures.

In *tabes mesenterica*, the glands of the mesentery and retro-peritoneum become enlarged and caseate; more rarely they suppurate or calcify. A slight tuberculous adenitis is quite common in children and is often accidentally found (post mortem). It may be a primary lesion associated with intestinal catarrh or secondary to tuberculous disease of the intestines. In adults tuberculous disease of the mesenteric glands may occur as a primary affection or in association with pulmonary disease. It may exist with tuberculous disease in the intestines or in any other part.

(b) *Tuberculosis of the serous membranes*. These are chiefly involved, simultaneously or consecutively. It may be acute or chronic or of the form in which the tubercles are hard and fibroid, the membranes much thickened and with little or no exudate. There may be no visceral association in these cases. The pleura, pericardium and peritoneum are affected.

Pulmonary tuberculosis. Three clinical groups may be recognised (1) acute pneumonic tuberculosis; (2) chronic ulcerative tuberculosis and (3) fibroid tuberculosis.

Acute pneumonic tuberculosis. The mode of onset resembles that of lobar or lobular pneumonia, but in some cases it is not quite so sudden. In children, acute tuberculosis often follows an attack of measles or whooping cough, whereas in adults, there has usually been a pulmonary tuberculous focus for some time.

Chronic ulcerative tuberculosis. Under this heading may be grouped the great majority of cases of pulmonary tuberculosis in which the lesions proceed to ulceration and softening. The general symptoms of fever, sweating and emaciation and local signs and symptoms are characteristic.

Fibroid tuberculosis. This form may come on gradually as a sequence of chronic tuberculous broncho-pneumonia or follow a chronic tuberculous pleurisy. In other instances the process may supervene upon ordinary ulcerative tuberculosis. The disease is chronic, lasting from ten to twenty or more years during which time the patient may have fair health. Modes of death in pulmonary tuberculosis are by asthenia, asphyxia, syncope, hæmorrhage or with cerebral symptoms.

Tuberculous laryngitis. Tuberculous laryngitis is usually associated with pulmonary tuberculosis. The disease may be localised to the vocal cords, interarytenoid space, ventricular bands or epiglottis. There may be swelling, infiltration or ulceration. The posterior part of the vocal cords is most often affected.

Tuberculosis of the alimentary system.

(a) *Lips.* Tuberculosis of the lips is very rare. It occurs as a solid tuberculoma or in the form of an ulcer either alone or along with laryngeal or pulmonary disease. The ulcer is usually very sensitive and may be mistaken for a chancre or an epithelioma.

(b) *Tongue.* The disease begins by an aggregation of small granular bodies on the edge or dorsum. Ulceration proceeds, leaving an irregular sore with a distinct but uneven margin and a rough caseous base. The ulcer is very indolent and is always secondary to pulmonary or laryngeal tuberculosis.

(c) *Salivary gland.* The salivary glands seem to possess a strong immunity and very few cases have been reported.

(d) *Palate.* Tuberculosis of the hard or soft palate nearly always extends from the neighbouring parts and the lesions are usually multiple and ulcerated.

(e) *Tonsils.* There may be infection of the crypts, superficial ulceration or an infiltration with miliary tubercles.

(f) *Pharynx.* In extensive laryngeal tuberculosis, it is not very uncommon to find an eruption of miliary granules on the posterior wall of the pharynx. Adenoids of the nasopharynx may be tuberculous.

(g) *Oesophagus.* This condition is very rare, and is a pathological curiosity. Slight extension from the larynx is not infrequent.

(h) *Stomach.* Many cases are reported which are doubtful.

(i) *Intestines.* The tubercles may be primary in the mucous membrane but are more commonly secondary to disease of the lungs, and in rare cases the affection may pass from the peritoneum.

In some European countries primary intestinal tuberculosis occurs most frequently in children in whom it may be associated with enlargement and caseation of the mesenteric glands or with peritonitis but the incidence of primary intestinal tuberculosis in India is small (5.1 per cent.) because of the rarity of infection of the cows. Secondary involvement occurs in chronic pulmonary tuberculosis. The lesions are chiefly in

the ileum, caecum and colon. The caseation and necrosis may lead to ulceration which may be very extensive. Perforation and peritonitis are not uncommon in the secondary ulceration. Extension from the peritoneum may excite tuberculous disease in the bowels. The affection may be primary in the peritoneum or extend from the tubes in women or the mesenteric glands in children.

Tuberculosis of the liver. This organ is very constantly involved in (a) miliary tuberculosis. In chronic tuberculosis miliary tubercles are not uncommon in the liver. (b) Solitary tubercle. Occasionally tuberculous masses are found, sometimes associated with perihepatitis, sometimes with tuberculous peritonitis and in children with tuberculous adenitis. (c) Tuberculosis of the bile ducts: This is the most characteristic tuberculous change in the organ and is not uncommon. (d) Tuberculous cirrhosis: In all chronic forms of tubercle in this organ there may be fibrous overgrowth. Hanot, who described several varieties, states that this condition may be primary. Practically it is very rare, except in connection with chronic tuberculous peritonitis and perihepatitis.

Tuberculosis of the brain and cord. Tuberculosis of the brain occurs as (a) an acute miliary infection causing meningitis and acute hydrocephalus; (b) as a chronic meningo-encephalitis, usually localised and containing small nodular tubercles, and (c) as the so-called solitary tubercle. In the spinal cord the same forms are found. The acute tuberculous meningitis is almost always cerebrospinal. The solitary tubercle of the cord is rare and usually secondary.

Tuberculosis of the genito-urinary system. Any part of the genito-urinary system may be invaded. The disease may be limited for a long time to the urinary or the genital tract. As a rule, only in the later stage does involvement of both systems occur.

Infection of the genito-urinary tract occurs in various ways. (a) Congenital, (b) by infection from areas of tuberculosis already existing, and (c) by infection from without. Urogenital tuberculosis is commonest between the ages of twenty and forty years. Males are affected much more frequently than females. Once the urogenital tract has been invaded, the disease is likely to spread rapidly. The lymphatics may afford a means of spreading of the disease but in the majority of cases the infection is haematogenous.

Kidneys. Primary tuberculosis of the kidneys is rare. In general tuberculosis the kidneys frequently present scattered miliary tubercles. In pulmonary tuberculosis it is common to find a few nodules in the substance of the organ or there may be pyelitis. In a majority of the cases the process involves the pelvis and the ureter as well, sometimes the bladder and prostate.

Ureter and bladder. This rarely occurs as a primary affection but is nearly always secondary to involvement of other parts, particularly

the kidneys. It may follow pyelonephritis or be associated with primary disease of the prostate or vesiculi seminalis.

Prostate and vesiculæ seminales. The prostate is frequently involved in tuberculosis of the urogenital system. The seminal vesicles may be involved primarily or secondarily. An extremely rare lesion is primary urethral tuberculosis. Chronic hyperplastic tuberculosis of the corpus cavernosum of the penis had also been described.

Testes and epididymes. This may be primary but more frequently is secondary to tuberculous disease elsewhere. In young children the testes proper may be involved first, but in adults the globus major of the epididymis is first affected. The lesion in the testes may heal completely or the disease may become generalised.

Fallopian tubes, ovaries and uterus. The fallopian tubes are frequently the seat of genital tuberculosis. The disease may be primary. The condition is usually bilateral. It may occur in young children. Tuberculosis of the ovary is always secondary. There may be an eruption of tubercles over the surface and an extensive involvement of the stroma with abscess formation. Tuberculosis of the uterus is very rare. It may be primary and occasionally the process extends to the vagina. Tuberculosis of the placenta is more common than has been supposed.

Tuberculosis of the mammary glands. There may be solitary or disseminated nodules, a sclerosing mastitis or caseation with abscess formation. The disease is most common between the fortieth and sixtieth years. It may be associated with tuberculous disease of the lungs, whilst a like affection may arise secondarily in the axillary glands; possibly in some cases the primary trouble lies in the glands, the breast being subsequently involved. Prognosis is not serious if total eradication of the disease is possible.

Myocardium. Miliary tubercles are sometimes met with in the acute disease. Large caseous tubercles are rare. The infection may pass from a mediastinal gland.

Endocardium. As a rule it is a secondary form, the result of a mixed infection, so common in pulmonary tuberculosis.

Arteries. Primary tuberculosis of large vessels is very rare and is usually the result of invasion from without. The disease however, may occur in larger arteries and not result from external invasion.

Chronic tuberculous endarteritis is met with in all places where tubercle is actively developing; in fact tubercles are often formed around arterioles and lead to their obliteration. The tuberculous endarteritis may however spread widely beyond the focus of mischief and in almost any portion of the pulpy granulation tissues this change can be seen.

Tuberculous disease of the bone. Bones may be affected in many ways by tubercle, the process starting either beneath the periosteum or more commonly in the cancellous tissue of the interior. The infection is secondary to disease elsewhere and the bronchial or mesenteric glands

are the commonest source of its origin. The osseous affection is often insidious in its onset and chronic in its course; it has a considerable tendency to involve the neighbouring joint and to give rise to suppuration.

Tuberculous disease of joints. This may commence either in the synovial membrane or in the articular end of the adjacent bone or it may spread to the synovial membrane from the periosteum as a result of tuberculous periostitis or from a neighbouring bursa. In children the disease commences most frequently in the epiphysis whilst in adults it may start either in the membrane or the bone with about equal frequency, but considerable variation occurs according to the particular joint affected. The disease usually commences in a most insidious manner. In the early stages with suitable treatment a complete cure may supervene with a movable joint; but later adhesions develop, with greater or lesser restriction of movement. Acute miliary tuberculosis may supervene as a complication at any time with a tuberculous affection of the lungs, brain, kidney or other viscera and may prove fatal.

Tuberculous disease of the spine. This disease most frequently occurs in children under the age of ten years; it has been shown that 60 per cent. of these cases are due to infection with the bovine type of organism in some countries of Europe; in India, bovine tuberculosis is rare. It may however occur at any age and equally in either sex. Any part of the spinal column may be involved but the lower dorsal is by far the commonest. The disease commences either as a periostitis or as osteomyelitis. Left to itself the disease usually progresses more or less steadily, the bone lesion becoming gradually more marked, and abscesses are likely to develop. If treated efficiently, repair by ankylosis may be confidently expected. As in tuberculous disease elsewhere the patient runs the risk of developing acute miliary tuberculosis. In spite of these possibilities the prognosis is good as regards life in cases free from complications and where suitable treatment is practicable.

Tuberculous disease of the skin (see skin disease).

Diagnosis. *Clinical.* In the early stage of infiltration, physical examination may fail to reveal any significant signs. Even when cavitation has occurred the signs may be absent or slight. For practical purposes more than 50 per cent. of cavities are absolutely or relatively silent, and if cavities are silent, it is obvious that areas of early infiltration may be equally so. If too much reliance is placed upon physical signs many early cases of the disease will be missed at a time when treatment might be effective.

X-ray. With great improvement in radiography the modern physician lays appropriate stress upon this as the most important method of obtaining more direct evidence. The modern skiagram shows the cardiac shadow with clearly defined margins, the compact though ragged shadows

of the glands and vessels of the lung roots, the trachea and its bifurcation, and the bronchovascular shadows spreading into the lung fields like the branches of a tree, and subdividing until as slender as silk threads they reach their terminal ramifications. The lung parenchyma between these striæ forms a delicate grey background against which any abnormality due to inflammation is easily detected. Radiology has shown that the common onset of pulmonary tuberculosis is an area of broncho-pneumonia situated below one or the other clavicle and revealed as a small area of coarse mottling in the centre of which a circular clear area may often be seen, indicating breakdown of the lung tissue with resulting cavity formation. Less commonly heavier shadows in the lower lobes reveal basal tuberculosis. Occasionally a film shows supraclavicular shadows due to apical tuberculosis, a relatively benign form tending to heal spontaneously.

Laboratory methods. Tuberculosis is one of the few diseases in which a diagnosis can often be made by microscopical examination alone. The simplest method is to stain a film of sputum, pus or other pathological product with Ziehl-Neelsen's stain. When the bacilli are present in very small numbers, attempts may be made to concentrate them by the antiformin method or by such methods as those of Faisca, Douglas and Meanwell, the last method is particularly useful for milk.

Urine should be centrifuged and films made from the deposit. With cerebro-spinal fluid it is best to allow the fluid to stand till a fibrinous clot forms; this should be removed, spread on a slide and stained in the usual manner. In both pulmonary and non-pulmonary tuberculosis the bacilli may often be found in faeces and for their detection some concentration method, such as antiformin or ligroin method should be employed. Tubercle bacilli may be found occasionally in the blood in advanced or miliary tuberculosis but the chances of finding them are very small indeed.

Cultivation is not often used in diagnosis but it may be useful when animal injection is impossible. The material should be obtained sterile and inoculated in Dorset's egg medium.

Animal inoculation. This is a most delicate test for the diagnosis of tuberculosis. The susceptibility of the guinea-pig to tuberculosis is extremely high, even minute amounts of infective material will cause infection in this animal. The material, sputum, pus, milk, etc., should be injected subcutaneously or intramuscularly into the thigh. In positive cases, in guinea-pigs so inoculated and killed after 3 weeks, there will be found a caseous local lesion, enlargement and caseation of the inguinal, sublumbar and portal glands and necrotic areas in the spleen and liver. It is advisable to inoculate two animals at the same time. If no signs of tuberculosis are apparent in the animal killed after 3 weeks the other should be kept 6 weeks after inoculation before being killed. In cases

of doubt, the suspected material or one of the glands mashed up in saline should be injected into a fresh animal.

Tuberculin tests. The two common methods are the single puncture method and the intradermal method of Mantoux. *The single puncture method.* Undiluted Koch's old tuberculin (O.T.) is used in this test. With ordinary aseptic precautions, a puncture about 3/16 inch deep is made on the anterior surface of the forearm with a sterile hypodermic needle, previously dipped in the concentrated old tuberculin solution. This introduces about 0.25 mgm. of tuberculin into the skin. A control puncture may be similarly made with another sterile hypodermic needle, a little away from the original one. The reaction following the puncture usually appears in two to four days. When positive, an area of erythema and oedema appears over the site where tuberculin was injected. *The intradermal tuberculin test of Mantoux.* Old tuberculin (O.T.) is also used in this test in dilutions of 1 in 10; 1 in 100; 1 in 1,000; 1 in 10,000 and 1 in 20,000. The skin of the anterior aspect of the forearm is sterilised with absolute alcohol and with a sterile 1 c.cm. tuberculin syringe, 0.1 c.cm. (0.1 mgm.) of old tuberculin (1 in 1,000) is injected intradermally. The initial dose in cases of recent hæmoptysis, cutaneous and joint tuberculosis, should not exceed 0.1 c.cm. of 1 in 10,000 (0.01 mgm.) old tuberculin. In positive reactions, an erythema extending to about 1 cm. develops in two to four days. Severe reactions result in swelling and even necrosis of the injected part. When positive reactions are obtained with higher dilutions, injections of stronger solutions of old tuberculin should be attempted to obtain similar reactions. The use of a solution stronger than 1 in 10 is not advisable.

The tuberculin reaction is a reliable test for hypersensitiveness to tubercle toxin and indicates past or present tuberculous infection. To exclude all tuberculosis, a negative reaction with a strong solution as with 0.1 c.cm. of 1 in 10 old tuberculin, is of proved value in clinical diagnosis. In children, a negative reaction excludes tuberculous adenitis, on the other hand the diagnosis of active tuberculosis with a positive reaction in a child under two years of age is suggestive. With complete calcification of tuberculous foci and destruction of the bacilli, the tuberculin reaction may be negative. King (1932) maintains that 90 per cent. of those showing a positive reaction to 0.1 c.cm. of 1 in 20,000 O.T. (0.005 mgm.) or smaller amounts have active clinical tuberculosis while those having arrested infection require large doses to show a reaction. Hart (1932) finds that patients suffering from latent bone and joint tuberculosis show reactions to minimal doses of tuberculin and that some patients with advanced disease require large doses to produce a positive tuberculin reaction. A positive Mantoux reaction, with indefinite physical signs in a child usually suggests some active focus of infection.

The determination of the *opsonic index* was introduced by Sir Almroth Wright as a method of diagnosis of tuberculosis. This is based on the estimation of the relative quantity of opsonin present in the serum of the suspected person as compared with that observed in healthy individuals. In man, in a certain proportion of early cases of pulmonary tuberculosis, the opsonic index might be low (a fact of diagnostic importance), while in other patients in this stage the index might be within normal limits. The results are variable and cannot be relied on.

The *complement fixation test* has been used with positive results in many cases of pulmonary tuberculosis, but on the whole the results do not give any indication as to the activity of the tuberculous process.

Serological tests. These methods of diagnosis are not satisfactory. The general consensus of opinion is that as methods of diagnosis they are unreliable. Many persons with tuberculosis fail to react while others who appear perfectly well do react.

The sedimentation of the red corpuscles of the blood has been studied in tuberculosis. Its rapidity is said to be increased in active pulmonary tuberculosis, and more so in the caseating and exudative types than in the fibrotic type of the disease. The sedimentation test assists in estimating the activity of or arrest of pulmonary tuberculosis, but is of doubtful value as a diagnostic test.

Prophylaxis. The preventive measures which are necessary to stamp out the disease might fall into three main categories: (i) Children with predisposition to tuberculosis need special care in their upbringing and such occupations should be chosen for them when they reach the age of puberty that they keep themselves in open air. (ii) Two great sources of tubercle bacillus are the sputa from infected cases and tuberculous milk; the latter is practically negligible so far as India is concerned. The former is a public as well as a private concern and all open cases should be isolated; this alone is an effective means of stamping out the disease. (iii) The third factor which resolves into a series of sociological questions lies in bad hygienic and economic conditions of life. Proper education and health propaganda will help the former question a good deal but unless the economical conditions of life improve very little gain can be achieved in this line.

The use of various types of antituberculosis vaccine is still in the experimental stage. Many attempts have been made to obtain satisfactory immunity by inoculation with human or bovine bacilli attenuated in various ways. Calmette advocated

a vaccine (B.C.G.) of a living culture attenuated by growth in bile, but immunization with B.C.G. vaccine cannot as yet be said to have established its claim as a preventive in man.

Treatment of pulmonary tuberculosis. The treatment is here considered mainly from the point of tuberculous affection of the lungs as this is the most commonly encountered clinical manifestation of tuberculosis. The treatment of other forms is more or less on the same principle. The tuberculous affections which need manipulative or surgical interference have not been dealt with.

General measures. Tuberculosis though a deadly disease is a curable disease if treatment is taken in hand early. Some are cured naturally without even realising that they have had tuberculosis. Sanatorium treatment in the true sense of the word and the increased use of collapse therapy and surgical treatment have increased the number of what are to all practical purposes 'cures' of tuberculosis. But people still die of tuberculosis and the demand still continues for a radical method of healing.

In the days when the early pathology of the disease was not properly studied and pulmonary tuberculosis was diagnosed only in its later stages, the treatment of consumption was based almost entirely on rest, open air, sunshine and nourishment, in which nature played the predominant part. This traditional routine is applied to all cases. Treatment is controlled by accurate temperature and pulse record; meals should be regular and ample. A total caloric value of 3,000 to 3,500 is usually required.

A liberal mixed dietary should be given, and solid food may be eaten during the febrile period. No attempts at over-feeding should be made. The Gersos-Hermandorfer diet, which has been widely used in Germany has not proved so successful in pulmonary tuberculosis as in the tuberculosis of skin and other tissues.

The essentials of this diet system are sufficient fresh vegetables, fruits and vegetable juices (uncooked), fresh milk (one pint or more daily), sour milk, eggs, especially the yolk; salt, fresh meat foods, oat meal and farinaceous foods should be

given in restricted amounts. The regime also includes two medicinal preparations ; mineralogen, a special blend of mineral salts of vegetable origin and a phosphoric acid and cod-liver oil preparation, both being administered thrice daily. Rest is the keynote, for the better the rest the better the chance of recovery. When the diurnal swing of the temperature does not exceed one degree and its acme be not above 98.6 and the pulse rate does not exceed 86, the patient is allowed up for one hour, and hour is added to hour until the patient is up for four hours when he is given some work (occupational therapy). Symptomatic treatment is given as required in a particular case.

Sanatorium treatment. This is recommended to suitable cases after the preliminary treatment but is totally unsuited for acute febrile or very active cases. The patient is kept under skilled medical supervision, his immunity being increased by food, fresh air, rest and exercise. His habits are changed under strict discipline. On arrival of a new-comer to a sanatorium he is kept in bed for a few days in order that his resting temperature may be observed and necessary examinations carried out. If there is pyrexia, rest is enforced till the temperature returns to normal. Then the system of graduated exercises is resorted to. After three months' stay it is usually possible to decide whether the patient is responding to treatment and if so, it should be prolonged for at least another three months or until the sputum is free from tubercle bacilli. During convalescence advice has to be given as to the best climate which will suit individual patients most, whether at home or abroad. One should clearly understand that it is not necessary to go abroad to be cured of tuberculosis.

Requisites of a good sanatorium. Sanatoria in India are of recent growth, the first one having been started at Almora in the year 1908. The plains in most parts of India being warm, it was thought that more elevated regions of the country would afford patients' protection from the deleterious effects of excessive heat on the tuberculous process. In a recent study made at Madanapalle Sanatorium (2,500 feet) it was found that the progress towards recovery was hampered during the summer and was favoured during the winter. During the last two decades, sufficient experience has been gathered in India as regards the benefit of a suitable climate in assisting patients towards recovery.

For achieving good results, selection of the site must be made after considering many important factors. It must be remembered that a modern sanatorium is no longer a home for rest-cure but is a hospital situated in a good climate and equipped with adequate facilities for the latest methods of diagnosis, treatment, recreation, and industrial and vocational training. Authorities with extensive experience of Indian conditions are of the opinion that the best altitude for Indian patients for applying sanatorium treatment is between 2,500 and 4,000 feet above sea level. The altitudes of some of the sanatoria in India are ; Bhowali in U. P., 6,000 ft.; Hill Crest in U. P., 5,000 ft.; Dharampur in the Punjab, 5,000 ft. ; Belair (Panchgani) in Satara, 4,500 ft. ; Madanapalle in Madras, 2,500 ft. ; Itki in Behar, 2,300 ft.

Having found a suitable altitude, the next point which should engage attention is the climate, *i.e.*, rainfall, humidity, the minimum and maximum temperature, the direction of winds and the presence of dust, mist and smoke in the atmosphere. The experience of Indian workers seems to favour a place where the patients from the plains can stay throughout the year, which is neither too wet nor too dry, and which is neither too warm nor too cold. The soil should be dry and the site sheltered with an abundance of pure, fresh air. A sanatorium should not be near a town or a factory, as dust from such places is likely to increase the tendency to useless coughing.

In 1931-32, of the patients admitted into the Madanapalle Sanatorium 95.7 per cent. of early and moderately advanced cases improved, and the disease was arrested in 84 per cent. of early cases and 30.6 per cent. of moderately advanced cases. From a study of the after-histories of over 2,000 patients discharged from this sanatorium, it has been shown that 51 per cent. of them were alive for 5 years after discharge and 46.5 per cent. were doing full work. We consider this a very satisfactory result under Indian conditions and one which compares very favourably with that in Europe.

Artificial pneumothorax. The first great advancement in the radical treatment of pulmonary tuberculosis was in the last decade of the nineteenth century when Forlanini in Italy and Murphy in America devised *collapse therapy* for the treatment of pulmonary tuberculosis. The introduction of air in the pleural cavity was practised over two thousand years ago by Hippocrates and the modern idea of introduction of air into the pleural cavity as a therapeutic measure in certain pulmonary affections was first held by Carson of Liverpool as far back as 1822. Forlanini in 1882 gave it a practical shape and the method of collapse therapy by artificial pneumothorax is now recognised all over the world as one of the best in the

treatment of certain cases (about 5 per cent.) of pulmonary tuberculosis. The therapy is of particular value in certain cases of pulmonary tuberculosis, bronchiectasis, localised abscess of lung and interlobar empyema. It has also been adopted for the relief of pain in dry pleurisy and for broncho-pneumonia in children. Its induction in pulmonary tuberculosis is advisable in cases of unilateral disease which remains pyrexial after absolute rest in bed for about a month, in hæmoptysis which cannot be checked by ordinary methods, in unilateral acute pneumonic tuberculosis and in certain carefully selected cases of bilateral disease. The principles underlying this treatment are rest, evacuation of the septic material which has collected in the cavities and bronchial tubes, and hastening the fibrotic process. The contra-indications to artificial pneumothorax are active bilateral disease, asthma, fibroid lung and visceral complications.

Technique. The apparatus commonly employed in the procedure consists of two glass bottles, one of which is graduated from 0 c.cm. to 1,100 c.cm., a glass manometer, a four-way glass connection, glass filters, glass tubes, rubber tubes and the pneumothorax needle. Riviere No. 1 needle, generally used for primary induction, consists of a blunt cannula with a thin edge for penetrating the pleura and a trocar for piercing the tissues of the chest wall. No. 2 needles are employed for refilling purposes. The whole apparatus should be sterilised before use. The glass manometer is filled with coloured water up to the mark zero. The glass bottles are filled half their volumes with coloured solution of perchloride of mercury (1 in 1,000). The patient should be lying near the edge of the bed with a pillow under the chest and shoulder to widen the intercostal spaces. About half an hour before the operation, the patient should be given an injection of morphia ($\frac{1}{4}$ gr.) to prevent pleural shock. The site of puncture should be the sixth intercostal space in the anterior axillary line. The skin of the region is made aseptic with absolute alcohol or tincture of iodine. A 2 per cent. novocaine solution is injected through the intercostal space right down to the pleura to prevent pleural shock. The patient should be warned against coughing during the operation. With the trocar in position, the No. 1 pneumothorax needle is pushed in through the anaesthetised spot for about 1 c.cm. or less if the patient is thin and emaciated. The trocar is then withdrawn and the cannula pushed through, down to the pleura. Oscillations in the fluid column of the manometer indicate the contact of the cannula with the parietal pleura. The cannula is then pushed into the pleural cavity, avoiding damage to the lung tissues. The fluid level in the manometer now falls below zero and the

oscillations are synchronous with respirations. The oscillations should be at least 3 to 6 cm. and are often as much as 10 cm. ; each cm. of fall of fluid in the manometer corresponds with a change of pressure in the pleural cavity of 2 cm. of water. By opening the clips attached to the rubber tubes, air is slowly admitted into the pleural cavity. Even when as much as 300 c.cm. of air has been introduced into the pleural cavity, the manometer still records a negative pressure. The needle is then withdrawn and the punctured site may be sealed with collodion and cotton wool. If cough is distressing, a large pad and a firm chest binder may be used to minimise extravasation of air into the extrapleural spaces. The amount of air in primary induction and the subsequent amount in refills depend in all cases on the personal factor of the patient. Usually the second refill is undertaken two days after the first and the third three days after the second. The interval of subsequent refills is gradually lengthened to a week, ten days, a fortnight and so on. About 400 to 500 c.cm. of air will suffice for a first refill otherwise a high intrapleural pressure might result in mediastinal displacement of viscera. Variations of the pulse, temperature and body weight should be recorded to judge the effects of collapse therapy. Radiograms are often essential to determine the degree of pulmonary collapse. Pleural shock, surgical emphysema, gas embolism in vessels, intrapleural effusions with subsequent pleural adhesions are the common complications in collapse therapy.

Oleo thorax has been recently introduced with advantage. The oil used consists of liquid paraffin or olive oil containing oil of gomenol (2 per cent.) Indications of oleo thorax are :—(1) pleurisy complicating pneumothorax, (2) obliterative pneumothorax or incomplete collapse of the lung, (3) as a substitute for pneumothorax and (4) pleuro-pulmonary perforations.

Apicolysis is a process in which localised collapse of the upper part of the lung is produced by separating the lung and the adherent pleural layers from the upper chest wall. It was much advocated in the past, particularly by German surgeons, but the results are not satisfactory.

Collapse therapy by *phrenic avulsion* has been practised during recent years with considerable success. This is the operation of removing the phrenic nerve in its entirety. The idea is to paralyse the diaphragm which then rises steadily for at least four months to a variable height. The collapse after phrenicotomy is not however as complete as in complete pneumothorax. It has the advantage however of being applicable in cases of pleural adhesion when air cannot be introduced into the pleural cavity.

Another surgical method of treatment of pulmonary tuberculosis is thoracoplasty. This may be partial or complete according to the number of ribs removed. Removal of ribs allows the softer parts of the chest wall to fall in thereby giving rest to the affected lung which

is gradually collapsed. Thoracoplasty must not be done too early nor yet too late and never as a last resort. It should be recommended in suitable cases when artificial pneumothorax is impracticable and phrenic avulsion is insufficient. Cutting the adhesions by thoracoscopy is not in vogue at the present time.

Chemotherapy. During recent years chemotherapy has been attempted in pulmonary tuberculosis. The striking efficacy of arseno-benzene preparations in the treatment of syphilis has stimulated much research work to find a preparation of heavy metal which will be equally potent in tuberculosis. There are two main difficulties in the chemotherapy of tuberculosis, (1) the devascularised character of the tuberculous foci, and (2) the resistant nature of the tubercle bacilli to penetration of the cell substance by chemicals. The power of the tubercle bacilli to resist the action of chemicals is well known. Though this is true, the fact that tuberculous lesions may undergo calcification by deposition of lime salts indicates that these foci are penetrated in some cases by substances in solution. By vital staining method the presence of such dyestuffs as trypan red or trypan blue has been demonstrated in the tubercle. Potassium iodide was found to enter freely into tubercles when injected. DeWitt working with various dyes showed that methylene blue penetrated the tuberculous focus and even stained the tubercle bacilli within it but it had no bactericidal property. Later, a series of investigations were carried out by various workers to find an actively bactericidal substance which would penetrate into the interior of the tubercles. Koch, so far back as 1890, showed that gold cyanide in high dilution would inhibit the growth of tubercle bacillus *in vitro* but was of no therapeutic value in the living animal. Chaulmoogra oil was found to inhibit the growth of the bacillus *in vitro* as gold did, but in clinical practice it had no demonstrable value. The same is true of sodium morrhuate which is often used in doses of 0.5 to 1 c.cm. of a 3 per cent. solution by injections. Cerium, manganese, cadmium, mercury and copper have been tried without success.

Gold. Koch (1890) showed that compounds of gold prevented the growth of tubercle bacilli in culture and gold-potassium-cyanide was for some time successfully used in

the treatment of lupus. Only the inorganic salts of gold were used in therapeutics till Feldt (1916) introduced a complex organic compound of gold which he named 'krysolgan' and more recently 'solganal,' an aromatic compound containing 36.5 per cent. of gold has been introduced. Mollgaard (1924) used 'sanocrysin,' an inorganic salt of gold, in the treatment of pulmonary tuberculosis with beneficial results. Simultaneously, other workers in France and Germany applied aurotherapy in the treatment of arthritis. Since then krysolgan, solganal and other salts of gold have been extensively used in the treatment of pulmonary tuberculosis, lupus erythematosus, leprosy and various streptococcal infections.

Pharmacological action. Like all other heavy metals, gold is a protoplasmic poison and the soluble salts of the metal possess bactericidal properties. The metallic salts such as the chloride, have irritating properties and cannot therefore be used on injured surfaces. Metallic gold, even in colloidal form is apparently not absorbed from the gastrointestinal tract, and when the soluble compounds are given by the mouth, only small traces are absorbed. After injection of a soluble salt, absorption is complete and rapid. Elimination is slow and occurs chiefly through the kidneys and to a lesser extent through the intestine and bronchial mucous membrane. Experimentally nephritis has been produced in rabbits by the injection of relatively large amounts of gold and in man, acute nephritis with all its symptoms has been produced by the use of gold compounds. When given by injection, gold can be recovered from the stool and there may be ulceration of the stomach and upper bowel as a result of its elimination through these organs. The part of gold that is absorbed is retained in the tissues for a long time. In experimental animals the bulk of the absorbed metal can be demonstrated in the spleen, the liver coming next in order.

Gold is much less toxic than most of the heavy metals. Neutral preparations are apparently not at all poisonous when given by the mouth. When given by injection, gold may produce erythematous, morbilliform and urticarial rashes. Solganal and especially solganal-oleosum is said to be much less toxic than other gold preparations. The general toxic effects resemble those of arsenic and both acute and chronic forms of poisoning are known.

Certain other effects of gold therapy have been observed in man. Initially there is improvement in appetite, digestion and general sense of well-being. Large doses may produce abdominal pain and distension with elevation of temperature and nervous excitement. Tendency to bronchitis, during gold therapy, has also been observed.

Therapeutic uses. The investigations of Mollgaard (1924) placed gold salts on a permanent therapeutic basis. He reported successful results following the intravenous injections of sodium-auro-thiosulphate, better known as sanocrysin. A certain amount of success in the treatment of pulmonary tuberculosis was obtained and the early cases of open infection of the lungs improved rapidly, but advanced cases did not stand the treatment well. It is claimed that gold penetrates the lipid substance of the the bacillus, gets into its body, kills and dissolves the protoplasm, at the same time producing direct immunising effects. There is no direct evidence to show however that these compounds are able to destroy tubercle bacilli, and even in such concentration as 1 in 2,500 in human blood, the tubercle bacillus grows just as well as when none is present. It should be remembered that tubercle bacilli are intra-cellular and are therefore less accessible to the action of drugs.

The most difficult point in gold therapy is the regulation of the dosage. The doses should be gradually increased, care being taken that the reaction caused by the previous dose has subsided. The reactions to gold therapy vary considerably in different individuals and it is necessary to find the optimum dose in each individual case. In some cases gold salts produce certain secondary effects such as fever, epigastric pain, rash and albuminuria; they are therefore contraindicated in renal and intestinal tuberculosis and also in advanced cases of pulmonary tuberculosis.

The following are some of the compounds of gold which have been used in the treatment of tuberculosis.

Sanocrysin. It is an inorganic gold compound containing the negatively charged ion ' $\text{Au}(\text{S}_2\text{O}_3)_2^-$ ' to which its therapeutic properties are due. It is very soluble in water, diffuses rapidly, is stable and decomposes slowly in the body. The dosage of sanocrysin, as now employed, is to give it in gradually progressive doses, beginning with 0.01 gm. intravenously and increasing it to 0.025, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4 and 0.5 gm. at weekly intervals. As soon as a dosage of 0.5 gm. has been reached it is inadvisable to increase it in Indian patients. In all cases the dosage should be regulated with respect to temperature, general condition and pulse of the patient, until a total of 4 to 5 gm. of sanocrysin has been given.

Toxic symptoms have been noticed after injections of sanocrysin in tuberculous patients. These consist of sudden rise of temperature with malaise and sometimes rigor. The urine on examination may reveal albumin but it is transient and soon passes off. Vomiting and diarrhoea may occur and among other signs that have been observed are skin rashes, neuritis, oedema of the face and eyelids. In order to avoid these toxic effects it is better to begin the treatment with small doses and at longer intervals. If, in any case, a reaction occurs the treatment should be suspended for the time being, and restarted with the original dose when all the symptoms have subsided.

The class of case that responds favourably to sanocrysin treatment is the exudative forms of tuberculosis with very little exudation. The exudative type and acute cases do not react at all well to treatment. The effects produced in favourable cases are complete disappearance of tubercle bacilli from the sputum, a general improvement in the clinical picture of the case with marked lowering of the temperature. Many favourable results have been published with regard to the effect of the drug in lowering the mortality in tuberculous cases. Clarke in 1929 found that after sanocrysin treatment of tuberculosis, the mortality rate was considerably reduced among the treated compared with the cases who had not received the drug. Heap (1929) also obtained encouraging results in patients of good physique with no involvement of the intestine. It seems therefore that the drug is effective in early cases and in patients of good physique, but in advanced cases and in intestinal tuberculosis it is a failure.

Solganal and *solganal B* are described as di-sodium derivative of p-sulphomethylamino-o-auromer-capto-benzene-sulphonic acid, containing 36.5 per cent. gold. Treatment is commenced with small doses; 0.01 gm. in cases where there is no fever and if there is a temperature the dose should be reduced to 0.0001 gm.; later the doses are increased gradually, two injections being given weekly. Laryngeal tuberculosis has also been successfully treated with the salt. Recently *solganal-B-oleosum*, an oily preparation of *solganal-B* has been introduced. It is said to form a deposit in the muscles and hence prolong the absorption of the gold. *Krysolgan* contains 60 per cent. gold, the indications for its use are as in the case of the gold salts generally. *Lopion*, another gold preparation, has the same action and uses.

Mode of action in tuberculosis. The way in which gold acts in tuberculosis is not known. It has been shown that dilute solutions of gold inhibit the growth of tubercle bacilli, but the addition of animal serum minimises the effect. Thus Sweany and Wasick (1925) working with sanocrysin showed that there was complete inhibition of tubercle bacilli in dilution up to 1 in 200,000, partial inhibition in 1 in 500,000 and slight inhibition in 1 in 1,000,000; but in strains of recently isolated bacilli, growth took place in dilution of 1 in 20,000. On addition of serum, the bacilli grew well in dilution of 1 in 1,000 of sanocrysin in

salt solution. Fry (1926) showed that sanocrysin in a dilution of 1 in 2,500 in normal human or ox blood, did not in any way alter the growth of tubercle bacilli *in vitro*. Similarly it has been found that tubercle bacilli grow just as well as in the plasma of patients after a dose of sanocrysin as in plasma drawn before the dose. It is, therefore, obvious that gold does not act directly on the tubercle bacilli either *in vitro* or *in vivo*, and therefore some other factors must be operating in the process. Davies (1933) states that gold may act in tuberculosis by stimulating some defensive mechanism in the patient, most probably the cells of the reticulo-endothelial system. It is well known that these cells have a great phagocytic power and gold by stimulating the reticulo-endothelial system increases the power of the body tissues to combat infection. In support of this, Feldt has shown that the action of solganal is greatly diminished by injection of substances which block the cells of the reticulo-endothelial system and by excision of the spleen.

Calcium. Calcium is largely used in the treatment of pulmonary tuberculosis either by the mouth, intramuscularly or by the intravenous route. The frequent use of calcium is based on the idea that the calcium content of the blood is low in tuberculosis and that this favours the growth and activity of tubercle bacilli. Careful experiments both in the laboratory and clinically on human beings have shown that calcium does not influence the course of tuberculosis. Even when large amounts of calcium chloride are injected intravenously the rise in blood calcium is temporary. The use of calcium has however been favourably reported upon in intestinal tuberculosis. An intravenous injection of 5 c.cm. of a 5 per cent. solution gives prompt relief in pain and discomfort when they are due to dietetic indiscretion or catarrhal condition of the bowel. When however the intestinal symptoms are due to extensive ulceration, amyloid infiltration or localized peritonitis and peritoneal adhesions, the chances of relief of symptoms are remote.

Tuberculin. Tuberculin was introduced by Koch for the treatment of tuberculous infection in man. An enormous number of different varieties of tuberculin' has since been prepared; they can be divided into five main classes:—(1) Concentrated filtrate of old broth cultures, (2) suspension of the bacilli, (3) preparations containing modified tubercle bacilli, (4) living attenuated cultures of the organisms and (5) preparations containing non-human types of the bacilli.

The name tuberculin should be strictly applied to filtrates of broth cultures, and tubercle vaccine to preparations of actual bacilli. The most important constituent of the former is a toxic body or antigen distinct from the antigens of the bacillary body. If tuberculin is used the patient is desensitized to the toxic agent contained in tuberculin while with tubercle vaccine immunity is produced against the bacilli.

Old tuberculin (Koch) is made from human or bovine strains; the bacilli are grown in glycerin veal broth in large containers and then incubated at 37°C; their contents are then strained through muslin or

paper-filters and the material evaporated to one tenth of its original volume. The tuberculin may then be heated to 100°C., the unconcentrated filtrate is sometimes used and known as T. O. A. The other important type of tuberculin is the bacillary emulsion (B. E.). Koch prepared B. E. by grinding living bacilli until all were killed, and this material emulsified in saline and diluted constitutes B. F. Some constituents of the tubercle bacillus have been shown to be toxic for animals, and many attempts have been made to eliminate the toxic material by extraction with acetone and digestion of the bacilli with trypsin, or with preliminary treatment with formalin. These preparations have, however, not been found to possess any advantage over those of the whole bacilli.

The success of treatment with tuberculin lies in the proper selection of the dose and of the interval between the doses. In the early days large doses of tuberculin were administered, but this had to be abandoned owing to toxic reactions and generalization of tuberculosis following such procedure. Tuberculin is now administered in so small a dosage initially that no reaction is produced; the dose is then repeated at short intervals and increased gradually so that no reactions occur. Wright and his followers advocate a scheme of dosage dependent on the changes produced in the opsonic content of the serum following injection of tuberculin. According to this scheme the dose depends upon the condition of the patient. If the patient is seriously ill, the dose must be small and should be frequently repeated, while if the lesion is circumscribed large doses may be given. The initial dose in cases of localised affections such as adenitis and arthritis is 0.00001 mgm. of tuberculin repeated at weekly intervals. Tuberculin is only given now-a-days to cases of the productive form of tuberculosis with a minimum amount of toxæmia, *e.g.*, tuberculous affections of the lymph glands.

The following general scheme of dosage is recommended.—

1st dose	1/4000	million of a milligram
2nd "	1/2000	" " "
3rd "	1/1000	" " "
4th "	1/500	" " "
5th "	1/200	" " "
given twice weekly,				
6th dose	1/100	" " "
7th "	1/50	" " "

at weekly intervals.

Doses in individual cases should, however, be modified according to the reaction produced.

The increase of the dose depends entirely upon the individual as well as the maximum quantity of the final dose. The relation of the quantity

of the final dose to the benefit derived from the treatment has not been worked out.

No patient should be given tuberculin who cannot follow this treatment for at least five months, although shorter courses seem to be of some benefit. In the more advanced stages a longer duration is required.

Symptomatic treatment. Besides the above treatments certain complications call for special treatment. The most important are (a) *Cough*. Certain amount of effort on the part of the patient aided by a sedative linctus containing syrup of phosphate of codeine or hydrochloride of heroin is all that is mostly needed to check the ineffective dry cough. If there is much secretion expectoration can be helped by sodium chloride 3 gr., sodium bicarbonate 5 gr., spirit of chloroform 5 min., and water to 1 oz., in 1 oz. of hot water. Night sweats may be distressing; the bed clothes should be light and the windows kept well open at night. A pill containing oxide of zinc 2 gr., and dry extract of belladonna $\frac{1}{4}$ gr. at night should be tried or subcutaneous injection of accoline 0.02 gm. once or twice daily. When the sweat occurs the patient should be sponged with toilet vinegar, the night clothes changed and a warm drink given. (b) *Hæmoptysis*. In the case of hæmoptysis if it is known from which side the blood is coming, to prevent the infected blood from being aspirated into the healthy lung, the patient should be inclined slightly to that side and propped up in a semi-recumbent position. Normal horse serum 10 c.cm. intramuscularly or 10 c.cm. of 10 per cent. solution of calcium chloride intravenously should be injected to stop the bleeding. Later, calcium should be given by the mouth. If the bleeding is severe and the patient cannot be calmed, a hypodermic injection of sulphate of morphine $\frac{1}{4}$ gr. should be given immediately. The morphine may be given up to a dose of 1 gr. within 24 hours if the bleeding still persists. When the bleeding cannot otherwise be controlled endeavour should be made to collapse the affected lung by artificial pneumothorax. All food should be taken cold and an aperient of sulphate of magnesia in 2 dr. doses should be given.

(c) *Diarrhœa*. This may result from irritation of the food, from toxæmia and amyloid degeneration or from tuberculous ulceration of the intestines. The diet should be reduced and consist chiefly of milk. Vitamins should be administered in the form of cod-liver oil $\frac{1}{2}$ oz. or other standard vitamin A and D preparations and tomato juice about 9 oz. a day. Lead and opium pill 4 gr. thrice daily or starch and opium enema can also be used for the relief of the symptoms.

For increasing the weight cod-liver oil and malt 1 dr. thrice daily after food may be given and with the hope of aiding the healing process in the lungs, collosol calcium and calcium chloride are recommended.

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CHAPTER VII

VIRUS DISEASES

Loeffler and Frosch (1892) discovered that when fluid from a vesicle in foot-and-mouth disease of animals is diluted and filtered through porcelain candles which hold back all visible bacteria, the filtrate retains its infective power unimpaired. Microscopic examination of the filtrate failed to reveal a micro-organism ; cultures on ordinary media also failed. This work was further supported by Iwanswsky and Beijerinck and thus was established the existence of a new class of infective agents. Many names have been given to the agent but none is entirely satisfactory. They have been designated as invisible microbes, ultramicroscopic viruses, inframicrobes, microplasms, strongyloplasms, chlamydozoa and filterable viruses. The name filterable virus has become the most commonly employed term, but since some of the genuine examples of the class are not filterable, and some other microbes, though filterable, are not viruses (*e.g.*, leptospira), it would be preferable to omit the word filterable and use the term virus as applicable only to this class of organism.

The viruses multiply illimitably in the tissues of an affected animal, but with the exception of the organisms of bovine pleuro-pneumonia the viruses have not so far been cultivated in a medium completely free from living tissue cells. The simplest theory of the nature of viruses is that they are living organisms. Stanley (1935) has succeeded in separating from the juice of Turkish tobacco plants, a crystalline protein having the properties of tobacco-mosaic virus. This substance produces typical tobacco-mosaic disease on inoculation into tobacco plants. At present there is no reliable information as to the size of the viruses.

Most of the viruses are relatively resistant to the action of 50 per cent. glycerol, differing in this respect from most of the visible microbes. Like ordinary bacteria all viruses are destroyed at high temperature. Phenol in 1 to 2 per cent. strength destroys many of them.

Some virus diseases, *e.g.*, small-pox, are extremely contagious while others like poliomyelitis are of low infectivity. They may occur in an epidemic form. The transmission of infection from the sick to the

healthy by means of insect vectors, including lice, ticks, mosquitoes, sandflies, mites and plant aphides, is illustrated by such diseases as typhus and trench fever (lice), Rocky Mountain fever (ticks), tsutsugamushi disease (larval mites), pappataci fever (sandflies), dengue (mosquitoes) and the plant mosaics (aphides). The epidemiology of certain forms of virus disease remains yet obscure. In herpes simplex, the most commonly held view is that the virus, while normally present, becomes active and produces its characteristic lesions only when the natural resistance of the body is reduced by some intercurrent infection (*e.g.*, pneumonia, common cold, etc.). A similar view has been held with regard to encephalitic sequelæ of measles, chicken-pox and vaccination against small-pox. Season plays some part in the epidemiology of virus diseases. For example, poliomyelitis is common in late summer while encephalitis prevails in the spring months.

The cell changes produced by viruses in the course of their interaction with the host tissues are variable. Within certain cells infected with some filterable viruses there occur atypical bodies or granulations, which are known as 'cell inclusions' or 'virus bodies'; such formation of inclusion bodies is characteristic in certain diseases, for example, Guarneri bodies in small-pox and Negri bodies in rabies.

Immunity. An effective and lasting immunity has been found to develop after an attack of certain virus diseases, such as small-pox, chicken-pox, mumps, etc. The immunity in the great majority of cases appears to last throughout life, but in some diseases, *e.g.*, herpes simplex and influenza, this immunity is not well-developed. Certain essential differences are said to exist between infections with a virus and bacterial infections, but it is probable that the mechanism of virus infection does not materially differ from that in bacterial diseases. Andrewes and others (1931) noted that in experimentally infected animals the virus of foot-and-mouth disease of cattle does not appear in the blood before the commencement of the febrile reaction, and after that it persists in the blood throughout the febrile period. Yellow fever virus has been shown to appear in the blood of monkeys 1 to 2 days after infection. The virus of vaccinia has been recovered from the blood after intradermal inoculation in the rabbit; similar investigations with highly potent strains of virus show that a generalised vaccinia may occur after dermal inoculations with a widespread eruption on the lips, tongue and in the internal organs. In certain respects, however, the virus diseases differ from bacterial infections; they have a tendency to localise in certain parts and to produce characteristic inclusion bodies in certain cells which have a marked bearing on the nature of immunity development.

Immunity to virus diseases may be active or passive. A passive immunity conferred by the administration of an antiserum prepared

from an animal is usually of short duration. Attempts have been made to confer immunity in virus diseases with the use of convalescent human serum, but the results are not as yet satisfactory. An active immunity on the other hand is nearly always produced by an attack of the disease, or it may be artificially induced. The latter is produced by the injection of a sublethal dose of living virulent virus, or a virus that has changed its character during adaptation to a different host, or a fully attenuated virus followed by injection of less and less attenuated virus until virulent virus can be given. Immunity can also be successfully produced by the injection of the killed virus; an example of this nature is Semple's carbolized vaccine used in rabies. Similarly there are records of successful immunization against many virus diseases in animals with vaccine containing dead virus, such as phenolized vaccine against cattle plague, formolized vaccine in foot-and-mouth disease of cattle, and against herpes and psittacosis by injection of formolized virus. It has been argued that the protection afforded by inactivated virus is temporary, but evidence at hand indicates that the injection of inactivated virus confers some degree of immunity if the method of preparation of vaccine is efficient. There is general agreement that certain methods of killing, such as subjecting to high temperature, may remove the antigenic value of some of the viruses. The usual method at present adopted is to give the living virus after partially immunizing the patient either with inactivated virus or with an antiserum. For the latter an effective method is the so-called site-to-site inoculation with virus and antiserum, that is, virus into one site and serum into another. Successful vaccination is generally indicated by a generalized reaction. It may also be produced by administering the antiserum after the injection of the living virus, and this is the method adopted at the present time in the prophylaxis of measles.

The mechanism of antiviral immunity is imperfectly understood. The fate of a virus when introduced into an immune animal is not known. Experiments so far made go to show that the viruses concerned in the production of diseases have special affinity for some tissues and are found there in greatest number. Vaccinia virus is found in the highest concentration in the lymph of the pustules, the virus of foot-and-mouth disease in the fluid of the vesicles, the virus of rabies or poliomyelitis in the central nervous system. In immunized animals the injection of a pathogenic virus is not followed by characteristic signs of infection, because of the virucidal property of the blood. In experimental vaccinia in rabbits specific antibodies have been found to appear in the plasma as early as the third day after infection; in case of yellow fever simultaneous presence of virus and protective antibodies in the blood has been observed on the 4th and 5th days of the disease. Analogous observations have been made with regard to many virus

diseases which indicate that there exists a definite clearing mechanism in the blood of all immunized and partially immunized animals.

The nature of the reaction that occurs in the blood in the production of immunity is still controversial. Most of our knowledge in this connection is derived from the work that has been done with vaccinia virus. The virus-containing material from the pocks of variola or vaccinia may give specific complement fixation or visible precipitation reactions *in vitro* with the serum of an immunized rabbit. Ledingham (1931) showed that the tissues of animals infected with vaccinia contain minute granules, the Paschen bodies, which are capable of agglutination by immune serum. Other investigations on this line have been carried out. Thus specific complement fixation with herpes virus and anti-herpes serum, with foot-and-mouth virus and the corresponding antiserum, with yellow fever virus and convalescent human serum, has been demonstrated by various workers. There is no doubt that both in an attack of virus disease in man and experimentally infected animals specific antibodies are produced. These antibodies form a sort of loose combination with the filterable viruses, but attain stability after a lapse of time and appear to be confined to the globulin fractions. A specific cellular immunity has also been suggested to explain the mechanism of antiviral immunity. In addition, as the reticulo-endothelial system is intimately concerned with the pathogenesis of virus diseases, it seems probable that it also plays an important part in the immunity production.

A scientific classification of the filterable viruses is hardly possible for want of knowledge of the essential biological characters of the members of the group, their mutual affinities and relationships. Our present knowledge is indirect, being finally expressed in terms of their pathogenic effects or the reactions they produce on their hosts. Joseph Fine has given a satisfactory classification on epidemiological and pathological grounds.

A. Diseases in which the virus possesses an intermediate host. They fall under two groups:—

- (1) The yellow fever group, including (a) yellow fever, (b) dengue and (c) sandfly fever.
- (2) The typhus group, including (a) typhus (*Rickettsia prowazeki*), (b) Rocky Mountain spotted fever (*Dermacentroxenus rickettsiæ*), (c) tick typhus, (d) trench fever (*Rickettsia quintana*) and tsutsugamushi fever.

B. Diseases in which the viruses are transmitted directly. They fall under four groups:—

- (1) The dermatropic group (affecting the skin or the mucous membrane only):—the viruses of (a) warts, (b) molluscum contagiosum and (c) trachoma.
- (2) The neuro-dermotropic group (affecting the skin and capable of

affecting nervous system).:—the virus of (a) herpes zoster, (b) varicella and (c) small-pox.

(3) The neurotropic group (affecting the nervous system only):—the viruses of (a) acute anterior poliomyelitis, (b) acute disseminated encephalo-myelitis, (c) rabies, (d) encephalitis lethargica and (e) disseminated sclerosis(?).

(4) The respiratory group (affecting the respiratory tract):—the viruses of (a) measles, (b) mumps, (c) influenza, (d) common cold (?) and (e) psittacosis.

TYPHUS AND ALLIED FEVERS

Typhus fever is an acute infectious disease, and is considered to be caused by *Rickettsia prowazeki*. Many typhus-like fevers have been described. Megaw suggests classifying the typhus group of fevers in the following way according to the nature of the transmitting agents:—(1) louse-borne typhus or typhus exanthematicus; (2) tick-borne typhus or Rocky Mountain fever. In India and many other places there is a typhus-like fever closely resembling Rocky Mountain fever. (3) Mite-borne typhus or Japanese river fever, which contrary to the idea suggested by the name, occurs in many localities of the Far East.

Rickettsia. The name Rickettsia has been used generically for certain minute bodies which are found in the gut of the infected lice. Da Rocha Lima proposed the name in honour of Ricketts, who first called attention to these bodies, and Prowazek, who further studied them. The name is also used for other very similar bodies, *R. quintana*, found in lice taken from trench fever patients and the species present in ticks infected with the virus of Rocky Mountain fever. The resemblances among these three species of rickettsia are very striking. Each of them is associated with a definite disease in man and is found in enormous numbers in the arthropoid host. In each species the size of rickettsia is very small, 0.5μ or less in diameter. They are non-motile, Gram-negative and stain feebly with aniline dyes, but can be coloured by prolonged use of weak Giemsa stain. *R. quintana* is found free in the lumen of the gut, *R. prowazeki* in the lining cells and the lumen of the midgut of pediculi and the rickettsia of the Rocky Mountain fever is present in the cells and lumen of the gut and other parts of the infected tick. The use of the name rickettsia has been extended to include minute forms found in many parasitic insects and arachnids. Many of these are, however, not pathogenic.

Da Rocha Lima (1916-19) made a careful study of the condition governing the appearance of rickettsia in lice and the association of these bodies with the virus. He maintained that rickettsia was a living microbe which was present in the blood but was unrecognizable microscopically. The presence of typhus virus in a louse can usually be detected by examining films of the midgut and its contents for *R. prowazeki*. The virus and the rickettsia are so constantly associated that it is an almost inevitable assumption that the virus is identical with the rickettsia. A louse which contains numerous *R. prowazeki* has always been found infective unless the louse has been dead some time, or both the virus and rickettsia have been killed as the result of treatment by heat, drying, or perhaps sometimes by the action of bacteria in the louse. *R. prowazeki*, like the virus, is not found in lice unless sufficient time has elapsed since they were first fed on the infected blood and kept at a suitable temperature.

TYPHUS FEVER OR TYPHUS EXANTHEMATICUS

Typhus fever is a louse-borne infection. It is a febrile affection which lasts for ten to fifteen days with a peculiar rash appearing on the body between the third to the fifth day. Though it is principally conveyed from man to man by the agency of the lice, other vectors may also play a part in its transmission. The disease is of great antiquity and is probably identical with many of the plagues described by the older writers.

A distinct advance as to the nature of the disease was made by Nicolle and Conseil (1910) who were successful in conveying the disease to monkeys by lice previously fed on typhus patients and they also successfully conveyed the disease from monkey to monkey and from rabbit to rabbit by inoculation with the blood of the infected animals. Ricketts and Wilder (1910) described rickettsia bodies as the causative organisms of the disease and later Da Rocha Lima fully worked out the nature of these organisms.

Nicolle showed that in typhus fever the blood is only infective during pyrexia and for one or two days later. Attempts to obtain active virus in filtrates have been usually unsuccessful. Feigin (1927) claims that at certain stages of its development the virus can pass through a filter.

It has been shown that after an infective meal the louse does not become infective for 7 to 10 days. The virus is much more concentrated in the louse than in the infected blood. The mode of entry of the virus from the infected louse has been the subject of controversy. Nicolle, Blanc and Conseil (1916) showed that the excreta of infected lice was highly infective, and Bacon and Arkwright (1923) concluded that the

mechanism of infection was by the contamination of a scratch with the lice excreta; they considered the bite an unlikely source of infection.

Active immunity is invariably established after an attack of the disease. The duration of immunity varies; in guinea-pigs it lasts a year or longer. Da Rocha Lima (1918), Weil and Breinl (1924) produced active immunity in animals by means of dead louse virus. Passive immunity can be conferred by convalescent serum after the febrile attack.

The agglutination test was first employed by Wilson, a modification of which is now commonly known as the *Weil-Felix test*. It is very reliable in most cases. This is carried out in the same way as the *Widal test*, but the organism which is used is *Proteus X 19*, which strangely enough has no association with the disease. A positive reaction in dilution of 1 in 100 is diagnostic. The reactions remain positive in dilutions of 1 in 50 or over for about 3 months.

TICK TYPHUS

(Rocky Mountain Spotted fever)

A few cases of typhus-like disease transmitted by the bite of ticks have been recorded by Megaw. This disease resembles Rocky mountain spotted fever, which occurs in the Bitter Root Valley of Montana and the neighbouring mountainous parts of Idaho, Wyoming and Nevada. As the tick typhus of India has not been thoroughly studied, the classical Rocky Mountain spotted fever will be described in detail.

Rocky Mountain spotted fever closely resembles typhus fever but the tendency to hæmorrhage and gangrene is greater in this disease. It is transmitted to man by the bite of the wood-tick, *Dermacentor venustus*, though contact of the skin with the contents of a crushed tick may cause infection. In the wood-tick the virus is transmitted from larvæ to nymph, from nymph to adult and from the adult through the eggs to the next generation. The natural hosts and reservoirs of the virus are certain rodents on which the immature ticks feed. The rabbit-tick *Hæmaphysalis leporis-palustris* also plays an important part in the dissemination of the virus.

The organisms commonly accepted as the cause of the disease are rickettsial bodies described by Ricketts and Wolbach. They are present in the blood of infected men, monkeys and guinea-pigs, and in the salivary glands, alimentary sacs, oviducts and eggs of ticks.

These organisms are known as *Dermacentroxenus rickettsi*. The virus does not pass through a Berkefeld filter and is destroyed at a temperature of 50°C; defibrinated blood remains infective for 12 days if kept at a temperature of 10°C. A period of some five days must elapse before a tick is capable of transmitting the disease after a feed of infected animals. Tick virus is more penetrating than mammalian virus and it can pass through unbroken skin. Guinea-pigs are easily infected by the inoculation of blood and by bites of infected ticks. White rats and monkeys are susceptible but domestic rabbits are not susceptible. Natural immunity is unknown but artificial immunity can be produced with a potent vaccine prepared from infected ticks but not from vaccine prepared from mammalian virus. Though rickettsial bodies have up till now been accepted as the cause of the disease, many workers have failed to find any correlation between the numbers of the rickettsial bodies and the concentration of the virus in the tissues. They conclude that *Dermacentroxenus rickettsi* probably represents only one of the several phases of the infecting agent.

Tick typhus of India. In India Megaw (1921) described a typhus-like fever which he believed to be due to the bite of a tick and later he described many cases presenting symptoms like typhus fever among men exposed to tick bites. The incubation period of the disease varies from one to three weeks, the temperature continues for twelve to sixteen days ending by lysis. The Weil-Felix reaction is variable and is usually of low titre. There is a striking resemblance between the Rocky Mountain fever and the tick typhus of India and the latter may be regarded as closely allied to it, if not identical. The points of dissimilarity between the tick typhus of India and Rocky Mountain fever are that in the former the spleen is rarely enlarged, albuminuria and jaundice are not seen, and that inoculation experiments fail to transmit the disease to guinea-pigs.

MITE TYPHUS

(Japanese River fever, Kedani disease or Tsutsugamushi disease)

This disease presents symptoms closely resembling those of typhus and is believed to be caused by rickettsia bodies. It has been known for a long time in Japan, being particularly prevalent during the summer and along the course of certain rivers. An identical though milder form of the disease occurs in Sumatra, Malay States and the typhus-like fever described by Ghosh in India and the *fièvre exanthématique* of the Mediterranean are probably of similar nature.

The disease is conveyed by the larvæ of certain mites, chiefly *Trombicula akamushi*; the adult mite is infected from wild rats and mice, the virus being transmitted to their larvæ which are capable of infecting human beings. The natural reservoirs are the wild rodents in which the virus persists throughout the winter though they may not show any symptom. Monkeys and rats can be experimentally infected by blood or tissues and also by the bites of mites or inoculation of their crushed bodies. In man natural infection occurs from the bite of mites; a sore develops at the site and is followed by a fever of 2 or 3 weeks' duration, enlargement of the neighbouring glands, a typhus-like rash, and leucopenia. The chief histological change is an increase of lymphocytes around the arterioles in the deeper layers of the corium. There are no specific changes in the internal organs. The virus occurs in the blood, lymphatic glands and in the mononuclear endothelial cells of the spleen, but it disappears early in convalescence. Plasma and serum do not contain the virus, and Kawamura (1923) reported that the polymorphonuclear cells remained infective even after repeated washing. It has not been shown to pass a filter. The causative organism is closely related to the Rickettsia bodies occurring in Rocky Mountain fever, and Sellards proposed the name of *R. nipponica* for it. Hayashi (1920) observed characteristic intracellular bodies at the site of the ulcer in man, and called them *Thellieria tsutsugamushi*. There is no cross immunity between this disease and typhus. The Weil-Felix reaction is usually negative but is sometimes positive in low titre with non-indologenic strains. No immunity seems to have developed after an attack, though repeated attacks have been known to render the subsequent infections less severe.

As the prophylaxis and treatment of the typhus group of fevers are conducted on the same principles, they may be considered together.

Prophylaxis. The prevention of typhus fever lies in measures adopted to avoid being bitten by lice. The body lice can be destroyed by thorough cleansing with a cresol bath. The clothes and dressings of the infected person should be sterilised; this can be done by exposing them to bright sunlight, by boiling or by the use of disinfectant lotions, such as, cresols and other coal-tar compounds; soaking in 2 per cent. lysol destroys both the pediculi and their eggs. A practical method of killing lice and their eggs is to expose them to a temperature of 55° C. for half an hour. Disinfection of the clothes on a large scale may be accomplished by super-heated

steam. It is also important to get rid of lice from the hair and bodies of those infected.

Vaccine. Attempts have been made to successfully vaccinate man against typhus fever. Though the typhus vaccine is yet in the experimental stage, the results so far reported appear to be encouraging. One method of vaccination consists in giving inactivated typhus blood. The blood of a patient in the acute stage of the disease is defibrinated and then incubated for about half an hour at 58°C. This is injected in doses of 1, 2 and 5 c.cm. at intervals of four to five days and is said to afford protection. Blanc and others (1933) prepared a vaccine with a living virus. The virus utilised in their experiments was a rat-typhus virus of low virulence. Several volunteers were inoculated with this virus and a mild reaction resulted. When later inoculated with a dose of the same virus there was no reaction at all. By treating the virus with ox-bile it was still further attenuated, although still active it produced a slight febrile reaction in man; those vaccinated were later shown to be immune to injections with epidemic typhus virus. Lice fed on these protected people did not become infected either after the immunising dose or the test dose, i.e., they did not become carriers of the germ.

Weigl has prepared a vaccine which has given good results in typhus fever. It is prepared by infecting lice with the blood of a case of acute typhus or from the blood or organs of an infected guinea-pig. The lice usually succumb to the infection in 9 to 10 days. The intestine is removed in a sterile manner, ground up in normal saline and a small quantity of 0.5 per cent. carbolic acid added. The dose is approximately 150 intestines per man divided into three doses. Weigl's vaccine has been largely used in Poland, some 6,000 persons have been inoculated. Of those who had received three doses of the vaccine none developed typhus although all were exposed to infection. Missionaries in China have also been successfully protected by this vaccine.

Weigl's vaccine affords protection to those inoculated and in some cases such people develop the disease, they

have a mild attack and are no danger to others since the virus is not present in the peripheral blood. Subsequent to the preparation of Weigl's vaccine, other workers prepared a modified form of this vaccine. Chrzanowski and Mosing (1933) found that rickettsia remains in the excreta of lice for very long periods. At first they used the excreta of lice which, however, produced a severe reaction and was therefore discarded. The method now employed is to emulsify the excreta in 0.5 per cent. carbol saline. A thick emulsion is formed which is centrifuged lightly and the supernatant fluid containing the rickettsia pipetted off; this is then centrifuged again at a high speed, the rickettsia is thrown down and the supernatant fluid drawn off; the sediment is then washed several times until a suspension of pure rickettsia is obtained. This vaccine compares very favourably with Weigl's original intestinal vaccine and produces just as good immunity. The employment of this vaccine will probably effect large economies both in time and personnel.

In case of typhus-like fever caused by the bite of a tick, avoidance of the bite is the best preventive. The infected part may be cauterized. Preventive vaccination is successful only in mild types of the disease; unfortunately the protection lasts for a short period.

With regard to mite-borne infection it is known that the virus is never transmitted from man to man. Cleanliness is of primary importance; destruction of field-mice and rats which harbour the infection should be undertaken whenever there is an outbreak. The field labourers should dust their bodies with sulphur powder to keep away the mites. Disinfectant lotions may be sprayed over them. A mixture of cajuput oil and tobacco juice, smeared on the skin is a good preventive. The body and clothes should be immediately washed on leaving the infected area. Special clothing may be worn.

Treatment. *Typhus fever.* The treatment of the disease is on the same line as typhoid fever. Strict attention should be paid to general hygiene, care of the mouth, and nutritious and easily digestible food should be given. The patient should be

in a recumbent posture and care taken to prevent any bed sores developing. Cardiac stimulants such as camphor and caffeine may be indicated. There is no specific drug known which is effective. Muhlens tried novasurol and reports that intravenous injection of novasurol in doses of 1 c.cm. in 1 per cent. solution appears to shorten the period of illness. Convalescent serum has been shown to have a curative effect in typhus fever. In experimental animals, such as guinea-pigs, the action of the convalescent serum (usually 10 days after the fever had ceased) is said to be specific. Jelin (1933) found that the effect was more marked when the serum was given early and in large doses, for instance, 24 to 48 hours after the injection of the infective material into guinea-pigs. The normal human serum, however, has little or no effect, while curiously enough, normal sheep serum possesses curative properties. Following the good results obtained with convalescent serum in animals, this has been used successfully in human cases. The only difficulty lies in obtaining a sufficient quantity of serum from human beings.

Serum from convalescent patients should be given in doses of 20 to 50 c.cm. It is said to lessen the severity of symptoms without having any effect on the duration of the illness. Nicolle's serum consists of serum from horses which have been immunised against the virus by injection of emulsions of spleen and adrenals of infected animals. It has given good results when given early in the disease. This serum has been tried intrathecally.

Rocky Mountain fever. The treatment is conducted on general principles as for typhus fever. Convalescent serum may be tried. Among the drugs used mercurochrome has been injected intravenously in 1 per cent. solution.

Japanese river fever (mite typhus). The treatment is on the same line as louse-borne typhus. Arsenical preparations such as salvarsan have been tried but have been found ineffective. Serum from cattle which have recovered from an attack, may prove beneficial.

INFLUENZA

Influenza is an acute infectious disease of disputed ætiology, characterised by fever, prostration, liability to pulmonary complications and to epidemic incidence.

There are several theories with regard to the ætiology of this disease. The earliest theory proposes Pfeiffer's bacillus as the cause of the disease. Experimental evidence has been advanced to show that Pfeiffer's bacillus is the cause of influenza. Blake and Cecil (1920) sprayed the nose and throat of 12 monkeys with cultures with partially successful result; but experiments on man have been less successful. This bacillus is, however, a very widely-distributed organism, and has been found in measles, tuberculosis, broncho-pneumonia and lobar pneumonia. It has been found in the healthy throats in 30 per cent. of cases in a series of students during non-epidemic times. Though it may be said that the virulence of Pfeiffer's bacillus may undergo periodic variations, evidence in favour of Pfeiffer's bacillus as the cause of the world epidemic of influenza in 1918 is very scanty. In the early stages of the epidemic Kristenson found this bacillus in very few cases, while Ledingham could not isolate it from any of his cases in Mesopotamia. In the later stages Pfeiffer's bacillus was commonly found, but this is the time when complications are frequently met with. Opie and others found that pneumococci and hæmolytic streptococci were even more prevalent than Pfeiffer's influenza bacillus.

Other theories embrace the view that influenza is caused by a mycotic organism, which has been found in the sputum, lungs, urine, blood and faeces in different types of cases. The organism appears to pass through various stages, coccal and bacillary forms, and at times shows the formation of spores.

That the disease is due to a filterable virus was first shown by Nicolle and Lebaillly (1918), who reproduced the infection in volunteers and in monkeys by the subcutaneous and intravenous inoculation of influenzal sputum passed through a Chamberland filter. These results were later confirmed by other workers. Filtrates of blood from influenza patients were also infective. Olitsky and Gates showed that the filter-passer was of the nature of a visible cultivable organism. A minute Gram-negative coccobacillus called *Bact. pneumosintes* was grown anaerobically and recovered only in the early stages of influenza in man and from the lungs of rabbits experimentally infected by filtrates of early influenzal sputum. This organism was not obtained in the normal throat, in non-influenzal conditions or in the later stages of influenza. Other workers failed to isolate this organism and found it in the healthy throat. It has been suggested that *Bact. pneumosintes* is not very pathogenic itself, but may favour secondary invasion by

Pfeiffer's bacillus and many other organisms, e.g., streptococci, etc., by lowering local resistance in the respiratory tract.

In recent years, evidence is again accumulating to implicate a filterable virus element in the causation of influenza. Dochez reproduced typical colds both in chimpanzees and human beings by means of the filtered nasopharyngeal washings from natural cases. Andrewes and Oakley (1933) had a like success in human volunteers with filtered nasal washings from patients with colds. Smith et al. (1933) produced in ferrets, fever and nasal catarrh by the intranasal instillation of filtrates of throat washings of influenza patients. Convalescent influenza serum was found to contain antibodies which prevented the disease in ferrets. This view receives strong support from the experimental work of Shope who found that a filterable virus is the essential factor in the causation of swine influenza. Though Shope's virus by itself produces a mild and transitory illness, association with *H. influenza* gives a complete picture of influenza. It seems that in epidemic influenza in man a filterable virus is closely associated. In certain cases this infection may facilitate the invasion of the body by many visible bacteria giving rise to various complications.

The disease tends to occur in pandemics about every 10 to 40 years, and in epidemics about every 9 months. The disease spreads with great rapidity and affects different strata of the population in different epidemics. In the 1889 pandemic, infants and old people were affected, whereas in 1918, young adults were chiefly the victims. The disease spreads with great rapidity.

The following clinical types should be recognised, and the treatment should, therefore, vary accordingly. The mild type is characterised by fever, pain all over the body, lassitude and sometimes epistaxis and vomiting. The severe or the respiratory type includes cases of pneumonia. The onset is like that of the mild type and pulmonary complications set in usually from the fifth day of the disease. A peculiar heliotrope cyanosis occurs in certain cases. The mortality rate is high in these cases (about 40 per cent.). The gastro-intestinal type of the disease is marked by vomiting, diarrhoea with blood in the stools; the fever when it persists is generally slight. The cerebral type of influenza is rare and is characterised by high fever, delirium generally of a low muttering type and ending in coma.

Prophylaxis. Owing to the fact that the causative agent of the disease is still unknown and its mode of transmission is not understood, complete success in prevention is not possible. It should be understood that the disease spreads rapidly by transfer of the infecting agent from one person to another. In an epidemic the virulence of the causative organism may be heightened during its passage from host to host. Isolation of

the patients should be practised wherever possible. Overcrowding increases the danger of infection as it favours transfer of the infected material and is the most potent cause in the spread of epidemic. Generally speaking the best course to adopt is to pursue a regular healthy life avoiding excesses of any kind.

The prophylactic treatment with drugs is without effect. Vaccines have been tried to prevent an attack, especially among children. In view of the fact that secondary bacterial invasions take place in the upper respiratory tract, efforts have been made to mitigate the severity and cut down the number of these infections by employing a vaccine composed of the visible pathogenic organisms. This is a simple antigenic mixture consisting of heat-killed cultures of pneumococci, *M. influenzae* and *Streptococcus hæmolyticus*. This is given at weekly intervals over a long period of time, about 8 to 10 injections being given before the winter and a similar number after it. This vaccination, though it has not been proved to be effective in preventing an attack, is claimed to have the power of reducing the severity of infection in those vaccinated. Other measures have from time to time been advocated, such as excess of vitamin A and D in the diet and irradiation with ultra-violet rays, but they do not in any way seem to diminish the chances of infection.

The Committee on the Preventive Measures of the Public Health Services, America, are of opinion that the following precautionary measures and practices of personal hygiene may be advantageous in the prevention of this communicable affection of the upper respiratory tract. (a) Crowds should always be avoided thereby lessening the chances of direct contact infection. (b) Any public assemblage or school and college need not be closed down, but they should be under strict medical inspection and any person or persons showing suspicious symptoms of the upper respiratory tract infection should be promptly isolated and no visitor should be allowed in such institutions and isolated communities. (c) Cleanly personal habits, and avoidance of all such acts as coughing, sneezing or spitting should always be strictly observed. Hands should be washed thoroughly before eating particularly by those who attend the sick. Adequate sleep and rest, avoidance of exposure to fatigue and any bodily excess, eating a moderate mixed diet and partaking freely of a sufficient amount of pure water, are measures to increase the general well-being of an individual. On these points of personal hygiene the prevention of such diseases depends.

Treatment. It is essential for the patient to take to bed early, as there seems to be a greater liability to pneumonic involvement in those who do not take early rest. The bed should be placed well away from the walls and the room should be large and well ventilated. Neglect of fresh air not only hinders recovery in the presence of pulmonary complications, but also tends to induce them. Fresh air is the most important factor in the treatment of influenza.

In the early stage the diet should consist of fluids only, later easily digestible solids are given. The patient is sponged regularly with tepid water. An initial dose of calomel followed by a saline purge should be given in all cases.

There is no specific drug for this malady. Dover's powder 10 gr. with aspirin 5 gr., at the onset, often relieves the early coryza. Quinine salicylate in 3 gr. doses, thrice daily, is helpful. A diaphoretic mixture with sodium salicylate is given for fever and pains. When the cough is troublesome local applications on the chest, throat paints and sedative mixtures are often of service. Inhalation of compound tincture of benzoin is very useful; failing this a spray containing chloretone and menthol, 2 per cent. of each, in liquid paraffin, may be used. In intractable cases relief may follow from the administration of a mixture containing syrup of chloral $\frac{1}{2}$ dr., ammonium bromide 20 gr., liquid extract of glycyrrhiza 20 min., in repeated doses.

Treatment is mainly dependent on symptoms and complications as they arise. The common complications are sinusitis, otitis media, mastoiditis, bronchitis and broncho-pneumonia. These should be treated on the usual lines. If pneumonia is due to type-I pneumococcus, anti-pneumococcal serum may be of service; convalescent serum has also been tried in these cases. The serum appears to have a specific effect in that the temperature begins to fall and there is considerable amelioration of symptoms. Many workers who used the serum, report rapid improvement in the general condition of the patient together with rapid resolution of the pneumonic condition. The usual procedure is to remove some blood by venesection and to inject

10 to 20 c.cm. of the convalescent serum intravenously ; this may have to be repeated. Cardiac stimulants should be started early if required.

Some authorities give antistreptococcus serum early in the disease in all bad cases, with favourable results. Besides these, many experimental methods of treatment were exploited during the pandemic of 1918-19, including various antiseptics intravenously but no remedy has yet been found successful.

Auto-hæmotherapy has also been recommended, 10 c.cm. of blood being injected intramuscularly and repeated twice. The occurrence of nervous complications should be recognised early. If symptoms of meningitis develop immune serum should be given. The convalescence should be carefully managed as relapses are frequent. Good food, fresh air, and tonics are indicated after recovery from illness.

DENGUE

This disease, also known as dandy fever and breakbone fever, occurs in many parts of the world. Dengue is characterised by a sudden onset, a diphasic febrile course lasting for 3 to 8 days, headache, severe pain in the body and limbs and rash. From time to time dengue fever assumes an epidemic form. It is caused by an ultramicroscopic filterable virus transmitted by the mosquito *Aedes ægypti*. It is not transmitted by *Culex fatigans*, the common culicine species.

Evidence has been produced to show that the disease is caused by an ultramicroscopic virus. Ashburn and Craig (1907) infected a volunteer with the filtered blood from a case of dengue. Other observers noted the infectivity of the serum of dengue patients. That the cause of the disease is a leptospira was suggested by Couvy (1922) and Carbonboa (1924) who reported the presence of spirochaetes in the blood and other fluids of the body, but the claim has not been substantiated. Sellards and Siler (1928) found numerous rickettsia bodies both in the lumen and epithelial cells of the hind gut of the infected *Aedes ægypti*. In the hands of most investigators the infective blood has failed to produce the disease in animals. The virus is introduced into the human body by the bite of the infected mosquito. Siler et al. (1928) passed the virus from man to mosquito and back to man through six generations without attenuation or increase in the virulence of the virus. They confirmed the transmission of dengue by *Aedes ægypti*. The pre-infective period in

the mosquito after an infective meal is usually from 11 to 14 days; the virus is not transmitted through the eggs of the mosquito. In man the incubation period by mosquito transmission is about 7 days but may be delayed till the tenth or the eleventh day. Ashburn and Craig (1907) found it to be $2\frac{1}{2}$ to 7 days after intravenous inoculation of 20 min. of the infective blood. It has been shown that the patient is most infective to mosquitoes from the first day of the disease, and by the end of the third day he is not, as a rule, infective. Cleland et al (1918) got successful results with blood taken between 18 and 90 hours and Manoussakis (1928) found the blood infective from a few hours before the onset of symptoms until deferescence.

Prophylaxis. In tropical climates the disease is mostly endemic because of the persistence of the *stegomyia* mosquito throughout the year, though it may be quiescent for a time and then flare up again. For an epidemic to spread in a certain locality, the factors concerned are: (i) the existence of infection in human beings or mosquitoes in sufficient numbers, and (ii) the existence of susceptible persons and suitable conditions of temperature and humidity. As the mosquito may remain infective permanently, there is a great danger to new-comers to an epidemic locality of being infected, thereby allowing the disease to spread rapidly. An infected person can also transmit the disease to distant places provided there are sufficient mosquitoes to act as reservoirs of infection.

These mosquitoes are essentially domestic and they breed in places in the immediate neighbourhood of human dwellings. Hence, if prophylactic measures are to be successful, steps should be taken for the destruction of mosquitoes and prevention of mosquito bites. As the virus of dengue is present in the blood of patients for about three days the patient should be protected from mosquito bites by proper screening during the period.

Prophylactic vaccination. It has been found that following an attack of dengue an immunity is established which may last for two to several years, but it has been known to be as short as 53 days (Siler 1926). Unlike yellow fever an attack of dengue does not give rise to protective properties in the serum nor is it possible to obtain a vaccine of the virus for treatment. Hence vaccine therapy has not been successful in protecting against

infection with dengue. Blanc and Caminopetros (1929) prepared a vaccine from killed virus which was ineffective ; better results were obtained with a virus treated with bile. St. John and Holt ((1931) prepared a vaccine from the spleen and liver of infected animals following the line of Hindle's vaccine for yellow fever. Though it did not protect a person from an attack, infection if it occurred was rendered mild.

Treatment. Dengue is hardly ever fatal. Treatment is mainly aimed at relieving symptoms. Dengue runs a definite course and all energetic measures to cut the disease short are useless. In the beginning of the illness a saline diaphoretic mixture may be prescribed. Antipyretic drugs such as phenacetin may be given for the relief of headache and backache and the high temperature should be brought down by hydrotherapy. Adrenalin has been recommended in dengue with the idea that it overcomes the asthenic stage and hastens the period of convalescence. Arsenical preparations have been tried ; acetylarsen in doses of 3 c.cm. by hypodermic injection or treparsol in doses of 1.0 gm. daily is said to abort an attack. Sulpharsenol has also been recommended.

SANDFLY FEVER

It is also known as phlebotomus fever, pappataci fever and three-day fever, on account of its being transmitted by sandflies—*Phlebotomus pappatasi*, and running its course for 3 days. It is caused by a filterable virus and is characterised by sudden onset, rapid rise of temperature with fall by lysis on the third day, headache, pains in the eyeballs and muscles, injected conjunctiva, bradycardia and leucopenia with a large mononuclear increase. Thus it simulates dengue clinically and they have been mistaken for one and the same disease but it is to be understood that an attack of sandfly fever never confers any immunity for the other disease and *vice versa*, and they have also a different geographical distribution.

The virus of sandfly fever is present in the patient's blood during the first 24 hours of illness. The blood has been found to retain its infectivity after passing through a filter (Doerr, 1908). This was later confirmed with different filters by other workers. Blood from a patient

taken within 24 hours of illness is capable of causing an infection in susceptible persons, but taken towards the end of the second day it loses its infectivity. At 55°C. the virus is destroyed in 10 minutes (Lepine 1927) but at 27°C. and in the dark it has been preserved for a week by Birt (1910). Attempts to transmit the disease to animals have failed. The usual vector is *Phlebotomus pappatasi*, but in addition, *P. perniciosus*, *P. minutus* and *P. sergenti* have been incriminated. The sandfly must bite the patient within 24 hours of the onset of the disease so as to be capable of transferring the disease to another. The incubation period in the sandfly is 7 days, but infectivity once established is permanent. Doerr thinks that the virus may be transmitted hereditarily by the insect to the egg. Wittingham and Rook confirmed the transmission from generation to generation.

Immunity is usually established after an attack of the disease, but it is rather short and a relapse or second attack may occur in 3 to 8 weeks. The serum of convalescents possesses definite protective powers. Doerr (1909) found this protective action in serum seven days after an attack and in one case, two years after an attack of fever. McCarrison (1915) was unable to infect 4 persons immunised with convalescent serum.

Prophylaxis. The prevention of sandfly fever rests on the measures against its carrier *Phlebotomus pappatasi*. Sandflies should be destroyed and their breeding places eliminated by spraying tar around habitations. Long boots should be worn after sunset, and electric fans, wherever possible, used to keep away the flies. An ointment containing oils of eucalyptus, anise and turpentine, 3 min. each, and lanolin 1 oz., applied to the wrists and ankles helps to keep away the flies. Mosquito nets are not protective as the flies can pass through their meshes.

Treatment. Treatment is carried on in the same lines as for dengue. Tincture of iodine should be applied to the bites. The patient should be kept in bed for 5 or 6 days and the pains relieved by antipyretic drugs, such as aspirin, etc.

YELLOW FEVER

Yellow fever is an acute non-contagious fever characterised by toxæmia, albuminuria, jaundice and a tendency to hæmorrhage. It is essentially a disease of the tropics especially tropical America and the west coast of Africa. Since the famous discovery in 1900 that this disease is transmitted by the domestic mosquito, *Aedes ægypti*, anti-mosquito campaigns seem to have

eradicated yellow fever from most of the endemic centres in the new world.

Noguchi (1919) described a leptospira known as *L. icteroides* as the causative organism of yellow fever. By the dark ground illumination method, a considerable number of these organisms was found in the blood, liver and kidneys of guinea-pigs inoculated with blood from certain yellow fever cases; further a pure culture of the organisms was obtained in an artificial medium and he successfully transmitted them through series of guinea-pigs. Later, the observations of other workers, including those of Noguchi himself, failed to substantiate the previous findings, as they failed to find any leptospira in a number of yellow fever cases. Kligler (1928) in Palestine found that *Aedes ægypti* which is the carrier of yellow fever could not act as a carrier of leptospira. Subsequently Stokes, Baur and Hudson (1928) in west Africa discovered that the monkeys of the species *Macacus sinicus* and *Macacus rhesus* could be easily infected with yellow fever with the production of symptoms and pathological lesions identical with human yellow fever, and they proved that the agent of yellow fever is ultramicroscopic and passes through Berkefeld filters. Convalescent sera from severe cases of yellow fever in doses of 0.1 c.cm. protected monkeys from further infection with the virus. Later, Sellards and Hindle (1928) showed that the virus maintained its virulence even when frozen, and they were able to infect a monkey with the frozen blood and liver of infected monkeys after twelve days. Hindle prepared a vaccine from the livers and spleens of infected monkeys which successfully immunised monkeys against enormous doses of the living virus.

In spite of numerous researches the causal agent of the disease is still under discussion. Recently, Kuczynski (1929) has announced the cultivation of a micro-organism from cases of yellow fever, and considers this to be the causal agent, but it has not been confirmed. In view of the results of filtration experiments, yellow fever is included in the groups of diseases caused by filterable viruses. It has been shown by several workers that the virus will pass through Chamberland filters when present in the circulating blood of man. The virus in the mosquito, on the other hand, is unable to pass through the filter. It has been suggested that the virus may have different morphology and dimension in the mosquito.

The work of the American Commission to Cuba established the fact that yellow fever is transmitted by the bite of the mosquito variously known as *Stegomyia fasciatus*, *Aedes argenteus* and *A. ægypti*. When fed on the blood of a yellow fever patient during the first three days of an attack, the mosquito becomes infected and after a period of twelve days is capable of transmitting the disease. Once infected the

mosquito remains so for the rest of life. The French Commission (1903) confirmed these findings and further found that infectious serum if heated for 5 minutes at 55°C. loses its virulence but has prophylactic and curative power. The infective serum becomes inactive in 48 hours, unless preserved under petrolatum when it remains virulent for 5 days. Cutaneous vaccination with the infective serum is without result.

Spread of yellow fever to India. The possible extension of yellow fever to new countries from the endemic foci is an important question which is attracting much attention. At the present time the complete absence of yellow fever from India is due to the absence of the virus. There is however clear evidence to show that the population of India has little or no immunity against the disease; the climatic conditions are also favourable for the development of infectivity in the insect vector, *Aedes ægypti*, which is prevalent in many places in India, especially in the principal ports. The introduction of the virus into any of the susceptible hosts, man, monkey or mosquito, might be enough to start an epidemic of the most alarming magnitude. Hitherto neither infected mosquitoes nor infected human beings have been introduced into this country, because the length of the voyage from infected countries has been an effective barrier. The introduction of rapid travel, especially by air, has changed the situation. It is now quite easy for an aeroplane to travel from West Africa or East Africa to India so rapidly that if a passenger had been bitten by an infected mosquito, he might be in a highly infective condition on reaching his destination. Hindle has found that *Aedes* mosquitoes sent from India are effective vectors, so there is no obvious reason why the disease should not spread like wild-fire in India and Far East if the virus was introduced by infected persons or mosquitoes. The situation created by modern rapid methods of travel therefore demands anxious consideration. The measures for the prevention of introduction of the disease to India are to take all rigid precautions against the conveyance of the mosquitoes from the endemic areas by aeroplanes, motor cars, trains, etc. Medical inspection of all passengers and crews for the detection of all possibly infected persons should be undertaken. Protective inoculation of all intending pilots and passengers in aeroplanes is a satisfactory method.

Immunity. Recovery from the disease is followed by a high degree of immunity. The duration of this immunity is fairly long, perhaps more than 5 years. Experiments with serum of both man and monkeys after recovery show that immune bodies are present in considerable strength. The serum of yellow fever convalescent patients, on inoculation, protects a susceptible animal against a fatal dose of the virus. This protective action appears on about the eighth day of illness. Passive immunity conferred by the serum usually passes off in about twenty days, though it may last longer. Convalescent serum when injected early to infected patients is said to diminish the severity of symptoms.

The presence of active immune bodies in the blood of recovered patients shows that the person has actually suffered from yellow fever, and this is a valuable test for diagnosis. For this purpose a monkey is injected with serum from suspected cases along with the virus. If infection occurs the case is probably not yellow fever. Effective protection is given by a vaccine prepared from the liver or spleen of the infected animal. The virus present in the tissue is destroyed by preserving it in 0.5 per cent. phenol or by simply keeping it in the ice chest. Two doses of such vaccine were found to protect monkeys for at least six months. Aragao used this mode of prophylaxis during epidemics in Rio in 1928-29.

Prophylaxis. The importance of the stegomyia carriers in the transmission of the disease is well founded. The Yellow Fever Commission found that the infection is conveyed by the bites of domestic mosquitoes. Carter later showed that two or three weeks must elapse after the introduction of a human infection into a place before the next group of cases can occur, owing to at least ten days being necessary for the development of the virus in the mosquito. Following strictly anti-mosquito measures, yellow fever has now been eradicated from Havana, Vera Cruz and Panama which were at one time the endemic foci of yellow fever.

To enable yellow fever to be controlled and eventually stamped out from an infected locality, energetic measures have to be carried out for the destruction of its vector *Aedes ægypti*. Connor in Guayaquil showed that a fall in yellow fever incidence coincided with measures taken to prevent contamination of tanks and water containers. The same worker reported equal success in Mexico, a certain area being freed from yellow fever by mosquito control. During an epidemic or during exacerbation of endemic yellow fever, non-immunes should immediately leave the locality. All cases of yellow fever should be reported to sanitary authorities. Any delay in recognising a case increases the danger of rapid dissemination of the disease and multiplication of infected centres.

Prophylactic inoculation. Experimentally, animals have been protected against yellow fever virus by injection of serum of patients recovered from the disease. Theiler (1931) tested the efficacy of immune sera against yellow fever virus in mice.

In his tests, the control animals all died, but the groups of mice used in tests of known immune sera behaved differently, some of them died while others survived. Sawyer and Lloyd (1931) using a different method in testing the efficacy of the protective sera obtained better results. In testing the sera, they etherised the mice lightly, injected starch solution intracranially and then injected a mixture of 0.2 c.cm. of the virus and 0.4 c.cm. of the serum intraperitoneally. A known immune serum completely protected the mice while in case of a non-immune serum all the mice died.

Workers in several countries have endeavoured, on the results of experimental evidence produced in support of immunity developed in yellow fever, to immunise human beings against yellow fever infection. The various methods that have been tried successfully may be classed as follows: (1) inoculation with immune serum; (2) inoculation with a vaccine containing killed or attenuated organisms; (3) inoculation with a mixture of virus and immune serum; and (4) inoculation with a biologically modified virus. The injection of convalescent serum from a recovered case of yellow fever, affords only a temporary protection; similarly vaccines containing killed or attenuated virus have given results of little promise. Simultaneous injection of a biologically modified mouse virus strain and immune serum has, on the other hand, given the best results in affording protection.

Findlay and Hindle (1931) recommended the use of combined living virus and immune serum for immunisation against yellow fever infection. They showed that whereas the duration of passive immunity rarely exceeded four or five weeks with immune serum alone, a more lasting immunity was obtained when a dose of virus was given at the same time as the immune serum, which in the case of monkeys has been tested up to a minimum of fourteen months. Successful vaccination of human beings against yellow fever has also been reported by Sawyer, Kitchen and Lloyd (1931). They gave by injection yellow fever virus attenuated by at least a hundred passages through the brains of mice, simultaneously with human immune

serum. Ten persons were inoculated, first a dose of dried mouse virus dissolved in distilled water being given, followed immediately by subcutaneous inoculation of immune serum in two places in the abdominal wall, the dose of the former being 0.03 c.cm. per kilo. and of the latter 0.3 c.cm. per kilo. body weight; they all developed protective power against yellow fever virus. Though as yet in the experimental stage, protective inoculation at present offers the most satisfactory method of immunity development.

Treatment. The treatment of the disease is more or less symptomatic. Experience has shown that a good purgative at the commencement of the attack is beneficial, *e.g.*, calomel in divided doses followed by a saline purgative. For cerebral congestion and headache, a hot mustard foot-bath may be employed. The feet and legs of the patient are immersed in a foot-tub full of warm water into which a pound of fresh mustard has been stirred. The bath should be kept hot during the whole procedure and a blanket kept over the patient and the foot-tub so as to favour free sweating. For high fever tepid or cold baths may be employed; antipyretic drugs such as phenacetin or antipyrin should be used very carefully because of the depression they produce. Vomiting, especially black vomit, is one of the troublesome complications that may confront the physician; it may be treated with a mustard plaster over the epigastrium and by giving the patient ice to suck.

During the first few days no nourishment is required; the patient should be allowed an abundance of fluid. About 30 gr. of sodium bicarbonate in a pint of water makes a good drink and may be given *ad lib.* There is every likelihood of acidosis developing in the course of yellow fever and all possible measures should be employed to check it.

As compared with other fevers the liver is characteristically affected in this condition. For such cases glucose should be given by the mouth whenever possible; in grave cases about 12 oz. of 5 per cent. glucose solution should be given intravenously.

Sternberg's treatment consists in giving 1½ oz. of a mixture

of 150 gr. of sodium bicarbonate and $1/3$ gr. of mercury perchloride in a quart of water every hour; this is very helpful in counteracting the hyperacidity of the gastric and intestinal contents. Strychnine may be indicated in the asthenic stage and camphor in oil should be given hypodermically whenever there is reason to suspect cardiac weakness. The diet should be prescribed on the lines employed in infectious fevers generally, and discretion and caution are indicated during the period of convalescence.

As regards specific therapy there has so far been none which can be relied upon. Neo-salvarsan in two doses of 0.15 gm. each at two hours' interval, is said to have given beneficial results. Noguchi tried anti-serum in the treatment of yellow fever but he used *L. icteroides* to immunise animals against yellow fever, which as is now known is not the causal organism of the disease, and trials of this serum in West African yellow fever have failed to prove its efficacy. Hudson, Bauer and Philip (1929) showed that convalescent sera from patients suffering from yellow fever protected monkeys from an infection with yellow fever and this finding may be useful for successfully preparing an anti-serum in the treatment of the disease in future.

SMALL-POX

Small-pox is an acute infectious disease characterised by fever and followed by an eruption which in about eight days passes through successive stages of papule, vesicle and pustule. A secondary rise of temperature occurs during the pustular stage of eruption. The disease is of great antiquity and of widespread distribution and occurs both endemically and epidemically. Rogers claims that the prevalence of small-pox in India depends upon the humidity and the temperature, i.e., the combination of high humidity with a high temperature is inimical to its growth. In India small-pox is responsible for an annual death rate of about 50,000; in recent years the case mortality has considerably decreased owing to efficient prophylactic vaccination which has modified the disease.

The disease in its typical form may be divided into four stages:—(1) The incubation period occupies 10 to 18 days. (2) The initial stage

of toxæmia lasts for 4 to 6 days with headache, giddiness, rise of temperature and petechial or purpuric rashes on the skin. (3) The stage of true exanthema is apparent about the third or fourth day. The characteristic rash appears on the face and hands, extending downward to the legs; later papules, raised and hard to the touch and reddish in colour take its place; then vesicles form and about the sixth day develop into pustules. Concurrently with these eruptions on the skin, lesions also appear on the mucous membrane of the nose, mouth, fauces, pharynx, larynx, trachea, bronchi, etc. (4) the stage of secondary fever manifests itself on the sixth or seventh day; from the eighth to the ninth day the lesions show signs of drying up and leave scales which separate and fall off about the fourteenth day. The secondary fever arises mostly as a result of the lesions of the mucous membrane of the respiratory tract where extensive denudation of the surface favours infection with pyogenic organisms.

There are two distinct types of the disease, the first is the classical type of small-pox with severe symptoms and a mortality rate of about 10 to 30 per cent., the second is the mild type or alastrim, in which the symptoms are much milder with practically no mortality. Ætiologically and in immunological reactions alastrim is indistinguishable from variola. Gordon (1925) found that materials from cases of alastrim and from those of variola alike gave the complement-fixation and agglutination tests to anti-vaccinia serum. Though these results were doubted by several workers they have substantially been confirmed by recent investigations.

Clinically small-pox presents several varieties. So long as the pocks remain distinct from one another the disease is termed *discrete* small-pox. In some cases the pocks are numerous and run together leaving hardly any healthy skin between them; the disease is then called *confluent* or *semi-confluent* small-pox. A form of modified small-pox or *varioid* occurs in cases where the person possesses a natural immunity, and where the virulence of the infecting virus is low. An acquired immunity conferred by a previous attack of the disease or by vaccination is also likely to modify the disease and render it milder. A *hæmorrhagic* type of small-pox has been described in which the hæmorrhagic state may come on before the stage of eruption or after it; hæmorrhage may also set in during the vesicular stage.

Ætiology and mode of infection. There have been many attempts to demonstrate a specific organism in small-pox lesions by ordinary bacteriological methods and many bacteria have, from time to time, been isolated but their exact ætiological role has not been established. The fact that the contents of a small-pox vesicle, though capable of conveying the disease, do not yield any visible micro-organism is against a bacterial hypothesis. Grunhagen first described amoeboid bodies in the vaccine lymph and in the contents of the small-pox pustules.

Guarnieri (1892) observed intracellular bodies in the lesions of the variola; these bodies have been called *Cytoryctes vaccinae* or *Cytoryctes variolae*. Guarnieri's views have, however, met with many dissentients. It has been argued that they are the products of the nuclei of the epithelial cells and leucocytes due to the action of the virus. Various other bodies considered to be of parasitic nature have been noted. Puschen drew attention to very numerous granules in variolous lymph and varicella and these granules were considered to be specific owing to the constancy of their presence and their absence elsewhere. These granules are infective and cultivable in tissue cultures, but it seems probable that they represent only a certain phase in the development of the virus.

It is now generally agreed that the specific cause of variola and vaccinia is ultramicroscopic and filterable. The viruses of vaccinia and variola are essentially the same, vaccinia having developed pathogenicity for bovines while variola is pathogenic to man. Attempts to prove the filterability of the small-pox virus have not been uniformly successful although active filtrates have been obtained by some workers. Levaditi and Nicolau (1923) succeeded in transmitting vaccinia virus through a collodion filter which is permeable to peptones and bacteriophage. The virus is widely distributed throughout the body when an infection occurs. Its persistence varies with the form of the disease; in vaccinia the scabs are virus-free in 14 to 15 days, but in small-pox the virus persists for 2 months. Cultivation of the virus *in vitro* has failed but tissue culture has been successful.

Infection takes place in nearly all instances through the respiratory tract, other modes of infection such as, direct ingestion of infected material or direct contact with the infected skin, are quite exceptional. The usual sequence of events is that the virus is coughed out in droplets which contaminate the air and thus infect the mucosa of the upper respiratory tract of the susceptible individual; from here it is distributed throughout the body. Another means of contamination of the air is by transudation of the virus through the skin, the organism reaching the surface by way of the sweat glands or hair follicles; this theory however lacks experimental proof. In cases of naturally acquired disease no local lesion arises at the site of contact of the infected material with nasal or buccal mucosa and this constitutes a fundamental difference between the natural and artificially inoculated disease. In the natural disease the virus apparently passes between the epithelial cells without affecting them, but its site of location is unknown. The constitutional symptoms in small-pox are undoubtedly due to elaboration of the toxin, but the presence of the virus in the blood and toxæmia are not always synchronous. The regular and rapid development of local lesions in small-pox suggests that multiplication of the virus occurs at those sites; a toxin is at the same time secreted

which inhibits the activity of the phagocytes and facilitates the growth of pyogenic organisms. From about the fourteenth day and onwards the pocks dry up and separate; the living virus is contained in the dessicated scabs and these are able to transmit the disease to a new host.

Immunity. Immunity to small-pox may be acquired by a previous attack of the disease, by variolation or by vaccination and revaccination. The immunity conferred by an attack of small-pox usually lasts throughout life and variolation also gives a similar immunity. That vaccination also protects against small-pox was first demonstrated by Jenner who showed that inoculation with cow-pox protects against subsequent inoculation with small-pox. Many investigations in this connection have been carried out and the results indicate that the material from the eruption of a small-pox case produces in calves a disease identical with cow-pox (vaccinia). If the virus is passed through the host of certain species, the activity of vaccinia virus is better maintained. After inoculation with vaccinia virus a lasting general immunity develops. In rabbits by whatever route the vaccinia virus is introduced, the animal becomes resistant within about ten days. The virus is rapidly taken up by the leucocytes and remains in the circulation for at least eight days. In monkeys after inoculation with vaccinia virus, perfect protection is obtained against variola and alastrim, but the protection afforded by variola or alastrim against vaccinia is only partial. Highest immunity is obtained if a living virus is used. Heat destroys the antigenic property of the virus very considerably, and it has been found that lymph heated to 100°C. has no immunizing effect at all. With raw lymph, immunity develops from the fourth day and becomes maximal about the tenth day.

Seat and nature of immunity. It is important in clinical work to form an estimate of the amount of immunity present in men after vaccination and revaccination. A practical method depends on the observation of immediate reaction produced; the earlier and less the reaction the greater is the immunity. The seat of immunity conferred by vaccination was at one time supposed to be confined to the ectodermal epithelial cells. The modern tendency is to regard immunity as general and humoral rather than local and cellular. It has been shown that the variolo-vaccine virus readily passes into the blood stream and can be found there within a few hours of the inoculation. From the blood stream it passes into the reticulo-endothelial system and becomes generalised throughout the body. Plotz (1927) on the other hand thinks that the immunity is dependent on two factors, the dose and the area involved. Others consider that it depends more upon the dose than area, though there is evidence to show that a minimal dose gives as strong immunity as a potent dose. Much difference of opinion exists as to the power of the killed

virus to produce immunity. Though immunity has been shown to result from the use of killed virus, on the whole there remains considerable doubt whether immunity of any practical value can be produced by the use of killed or attenuated virus.

Recently, much work has been done on the nature of specific antibodies produced by vaccination. Specific variolical antibody was first discovered by Sternberg in 1896. This antibody has been shown to be closely related to the production of immunity. After an attack of the disease, these antibodies may persist for years, and are said to be enhanced after revaccination. Andrewes (1926) found no evidence that the virus was killed by the antibody and no stable union was found to exist between them. Many observers have recognised the presence of a precipitating antibody in immune variolo-vaccine sera. Gordon (1925) obtained evidence of definite agglutination with immune sera and a calf-lymph antigen diluted 1 in 20, with rabbit-lymph antigen in dilution of 1 in 140, and also with variolous material. Complement fixing antibody has also been found by many workers and positive complement fixation tests are reported. This is however doubted by others who obtained no evidence of specific complement fixation when immune sera prepared from the rabbit with pure brain virus were tested against cutaneous vaccinia or brain virus antigens. According to them these reactions are due to the presence of concomitant bacteria.

Laboratory diagnosis. The diagnosis of small-pox offers no difficulty from clinical signs and symptoms. Two tests can be employed for diagnosis; the first is the intracutaneous inoculation of variolous material into unvaccinated rabbits in whom characteristic local swellings develop on the second day reaching their maximum about the fourth day, the lesions disappearing by the twelfth day. Paul's test consists in the production of keratitis in rabbits after inoculation of variolous materials into their eyes. Recently, a serological method of diagnosis has been developed. A suspension of ground up variolous material is mixed with an antivaccinal rabbit serum and incubated at 37°C.; a positive reaction is marked by the appearance of a finely floccular precipitate. The complement fixation test can also be done.

Prophylaxis. *Vaccination and revaccination.* Small-pox is a preventible disease and the advent of vaccination has greatly reduced the incidence and mortality of the disease. It is well known that the incidence of small-pox is entirely amongst the unvaccinated and when the vaccinated are attacked death occurs amongst only those who have outworn their primary vaccination protection. Even when through lapse of time or otherwise complete protection against an attack is lost, the power of

modifying an attack still remains so that the disease assumes a modified form.

The pustules of vaccinia emulsified in glycerolated saline constitute vaccine lymph and is largely used for vaccination. For human vaccination though calf lymph is generally employed, it has been shown that lymph taken from vaccinal lesions in other animals gives satisfactory results. The usual procedure of vaccination is to vaccinate in a single linear incision or scratch, not more than $\frac{1}{4}$ inch long, through the epidermis. Other methods of vaccinating are the multiple punctures or pressure method through a drop of vaccine ; the drill method, in which a superficial layer of the epidermis is removed ; the method advocated by the Union of South Africa is to make two or three parallel incisions, $\frac{1}{4}$ inch long and $1/16$ inch apart, through a drop of lymph, such incision being single or multiple. Vaccination may be through a drop of lymph or the lymph may be applied to the trauma either simply or gently rubbed in ; the former gives less local reaction. In all cases the procedure should be treated as a surgical operation and rigorous precautions should be taken against sepsis. The vaccinated surface should be protected from dirt and injury.

After vaccination there is an incubation period lasting about 3 days during which little change occurs at the inoculated site. A localised papule develops on the fourth day which becomes vesicular on the seventh or eighth day and matures on the tenth or eleventh day, followed by scarring and pitting, popularly known as foveation. The vesicles begin to dry up at about the eleventh day and the process is completed by about the fourteenth, the scabs falling off normally about the twenty-first day. Slight febrile disturbance may be noticed as vesiculation proceeds, with headache, malaise, enlargement of the axillary glands, and in some instances of the spleen. In revaccination the degree of reaction depends on the amount of immunity remaining after the primary vaccination. The less the immunity, the closer the revaccination approaches to a normal primary vaccination, and the higher it is, the less is the local reaction.

Strong evidence exists as to the protection afforded by

vaccination against small-pox and this holds true particularly with regard to protection against infection. Vaccination performed immediately prior to exposure to small-pox affords almost absolute protection against the disease; if done during the incubation period, it either prevents the development of small-pox or renders the subsequent attack mild. Similarly recent successful revaccination is said to afford an almost complete protection. The first vaccination should be performed between the fourth and sixth month of life and immunity lasts for 10 to 15 years. As the effect of vaccination appears to wear off with increasing age, it is advisable to perform revaccination at about 10 years and again at the age of twenty.

Complications of vaccination. Of the common complications of vaccination suppuration and tetanus may be mentioned. The introduction of putrefactive organisms to the inoculated site occurs either through incomplete sterilization of calf lymph or uncleanness on the part of the operator, or during after-treatment. Tetanus is a rare complication. A more serious complication is post-vaccinal encephalitis. After an incubation period of 10 to 14 days it ushers in with acute symptoms, mainly pointing to the affection of the cerebrum. The cause of encephalitis is unknown; it has been suggested that the disease is similar to that seen in encephalomyelitis following measles and in disseminated sclerosis, being caused by some neurotropic virus which is stimulated into activity either by vaccination or by some exanthematous infection. McIntosh (1928) believes encephalitis to be due to vaccinia virus itself.

Besides compulsory vaccination in endemic and epidemic areas, other methods should be adopted so as to prevent dissemination of the infected material from the sick person to those around him. It should be realised that infective material exists in the eruption and may be carried through the air, and persons coming in contact with the patient may themselves be infected or carry and retain dangerous material. The first step towards prophylaxis, when a case occurs, is to isolate the infected person and treat him in a hospital specially meant for the purpose. The infected premises and the infected clothing should be thoroughly disinfected. The small-pox patient should not be discharged from the hospital until all infected epidermis is removed.

Treatment. The treatment is mainly symptomatic. In no

disease is the careful management of the patient so imperative as in small-pox. Abundance of fresh air, cool surroundings, fluid diets, regulation of the bowels, tepid sponging are essential measures. In the *initial stage* the patient often complains of headache and pain all over the body. Lumbar pain is relieved by poultices or dry cupping ; small doses of aspirin or pyramidon may be prescribed to relieve headache. It is always advisable to crop the hair short or have the head shaved because it helps to maintain cleanliness and gives a better opportunity to make necessary applications.

The mouth and throat require almost constant attention. Antiseptic gargles and demulcent drinks are to be frequently given, especially when there is difficulty of swallowing. In the latter case it is helpful to spray the throat with 1 per cent. solution of cocaine or orthoform. The eyes should be frequently bathed with some antiseptic lotion, such as boric acid. Protargol or argyrol solution may be dropped into the eye once daily. Many eyes are lost due to development of corneal ulceration, but if detected early it yields to treatment. An ointment of yellow oxide of mercury with atropine should be applied twice daily should keratitis threaten. For sleeplessness and delirium and to allay discomfort of the secondary fever, opium is the drug of choice. Dover's powder in doses of 10 gr. should be given twice daily ; morphine may have to be given hypodermically. Chloral hydrate and bromides as sedatives are also useful.

In the *eruptive stage* the patient should be sponged, and this is especially valuable when the temperature is high and is accompanied by severe toxæmia and delirium ; tepid sponging has sometimes to be replaced by cold packs. In less severe cases a bath (at 98°F.) may be employed and a solution of potassium permanganate added to it. In the early stage of eruption cold wet applications give much relief ; a mask soaked in glycerine may be applied ; a carbolic acid compress is also useful. Some advocate the painting of the face with dilute tincture of iodine once or twice a day for the first 8 or 10 days and then vaseline, but it is better to use a 5 per cent. solution of potassium permanganate twice or three times a day until scabbing begins ;

after this it should be used less frequently. Many methods have been tried with a view to aborting the eruption and preventing pitting but none are effectual. Finsen recommended exposure of the patient to the effect of red light in order to prevent suppurative changes in the pocks, but this is too depressing. To mitigate the offensive odour emanating from the skin lesions dilute carbolic acid lotions may be used; starch poultices and alkaline washes are used for the removal of crusts.

Complications should be treated on the usual lines. Heart failure is combated by strychnine, digitalis, etc. Hæmorrhagic small-pox unfortunately proves invariably fatal. Convalescence must be prolonged, and patients are to be regarded as infectious until the scabs are separated and the skin condition improve.

RABIES

This is a cosmopolitan disease, which is caused by the bite of certain rabid animals. While in nature, the incidence of the disease is heaviest in the canine tribe (dog, wolf, jackal, fox, etc.), other animals can be experimentally infected. The causative agent belongs to the group of filterable viruses which travel along the nerve trunks from the site of the infection. Development of symptoms depends on the time taken to reach the central nervous system. The incubation period therefore varies with the distance to be travelled; in man, for a bite on the head, it is approximately twenty-seven days, on the arm thirty-two days, on the leg sixty-four days, but these figures are subject to wide variations.

The properties and mode of action of rabies virus were very thoroughly worked out originally by Pasteur himself. On the basis of experimental work he described two forms of the disease which he ascribed to different modifications of the virus, termed 'street virus' and 'fixed virus.' The street virus was simply the infective agent of rabies, which is met with in the infecting fluids or tissues of animals developing rabies under natural conditions, and was proved by its transmissibility to be a living entity. Such virus inoculated subdurally into a rabbit produced the disease after an incubation period of fifteen to twenty days. With repeated subdural inoculations from rabbit to rabbit, the virus gradually altered its character, giving a shorter period of incubation until, after fifty passages, the incubation period was six to seven days. This was called 'fixed virus' by Pasteur. At this stage

the virus has become fixed and permanent and the change is an irreversible one. The essential differences are its reduced pathogenicity for man by subcutaneous injection, non-occurrence of Negri bodies and shortening of the incubation period. The view generally held is that the neurotropic virus, in becoming fixed, has become more habituated to growth in association with a cellular nervous tissue, and less able than street virus to establish infection by subcutaneous implantation. Remlinger (1928) is inclined to the view that the germ exists in the saliva in a different form to that in which it is present in the brain. There is however very little difference in the disease, once produced, whether by the street or fixed virus.

The essential pathological feature of rabies is the occurrence of 'Negri bodies', discovered by Negri in 1903, and there is little doubt regarding their specificity. Various opinions have been expressed as to whether the Negri body is a parasite itself, a degeneration developed around the parasite or reaction on the part of the nucleus of the nerve cell to the parasite. It is found most constantly in the ganglion cells of the cerebral cortex, chiefly in the hippocampus major, which is now regularly examined for the diagnosis of rabies. There may be one or more bodies in the cell; they vary in size from 1 to 15 μ , and contain within a capsule 20 to 25 rounded bodies; in the centre of each of these bodies is a corpuscle. The Negri bodies are more prominent in the later stages of the infection, progressively diminishing in size as the street virus becomes transformed into the fixed virus, until they finally disappear. The position as to the true nature of the Negri body was judiciously summed up at the recent International Conference on Rabies, where the decision was reached that insufficient evidence existed to determine whether the Negri body was a parasite or merely a cell product.

The virus is primarily associated with the central nervous system, but later on the salivary glands, the pancreas and the intestinal glands become infected. The blood is never infective. In the dog, the saliva becomes infectious four days before the onset of symptoms. Poor and Steinhardt (1919) showed that the filtrate of glycerinated salivary gland was infective, and Remlinger found that the virus could pass through a Berkefeld filter. Cultivation of the rabies virus has not been successful.

Of the various modes of transmitting the disease experimentally, the most certain is the subdural or intracerebral route and the least certain is the intravenous. The subcutaneous route, which is the route of natural infection, yields fifty per cent. of positive infections. Scarification is rarely successful, and therefore infection by licking of an abrasion by a rabid dog is very unlikely, while infection through intact skin or mucous membrane may be considered impossible.

In man, the course of the disease is similar to that in the dog. Fear and anxiety are prominent features from the onset. As the

disease progresses excitability increases. Sight of water or the very thought of it or the sound of running water will bring on pharyngeal spasm. Respiration becomes laboured and noisy; consciousness remains practically till the end. Paralytic manifestations follow the excitable state, and death occurs within 3 days of the onset.

Immunity. It is natural only in cold blooded animals and may be acquired in susceptible animals by treatment with attenuated virus. This can be conferred prior to infection or during the incubation period after the infection. Pasteurian treatment is therefore both a prophylactic and curative treatment. Pasteur's original desiccated cord treatment for production of immunity is hardly used now. With the recent discovery that the dead virus forms as effective a vaccine as the living virus, carbolised or etherised cord has been employed. The great advantage of the dead virus vaccine is the elimination of neuro-paralytic accidents. Passive immunization in rabies is hardly of any value and hence it is doubtful whether anti-rabic serum has got any antitoxic character. Such a serum however has been used in conjunction with antigen as a sero-vaccination method of treatment.

Prophylaxis. It is important to insist on muzzling of dogs and of quarantining imported dogs. A dog bite should be allowed to bleed freely, and then washed with 1 in 1,000 perchloride of mercury solution and cauterised with strong nitric acid. If there is any suspicion that the dog is rabid, the patient should be given Pasteur's treatment.

Preventive inoculation. It has already been stated that the power of the virus is altered when passaged through the nervous system of certain species of animals. By inoculation of the virus into rabbits its virulence can be increased up to a certain strength beyond which no further exaltation can be obtained and this is known as the 'fixed virus.' For the preparation of such vaccine rabbits and sheep are inoculated subdurally with this fixed virus daily. After death the spinal cord is removed with aseptic precautions, cut into pieces and suspended in caustic potash solution and kept in a dark room at a constant temperature of 23°C. Cords of different days and hence containing virus of varying degrees of virulence are obtained. The usual dose is a portion of cord 2 to 3 mm. in length prepared by trituration and suspension in salt solution.

This original method practised by Pasteur has now been greatly modified. Pasteur began his treatment with fixed virus which had been dried for fourteen days. Other workers have found that it is

not necessary to begin with such extreme attenuation of the organism as the fixed virus is greatly modified in its virulence for men. In fact, many observers have advocated the use of unmodified virus in large doses. Hogyes thinks that satisfactory results can be obtained by dilution of the fresh fixed virus with salt solution. He uses dilutions varying from 1 in 100 to 1 in 1,000, beginning with the highest dilution and reaching the lowest between the fourteenth to the twentieth day according to the severity of the case. Babes used spinal cord heated to 80°—60°—45°C. for 10 minutes in order to attenuate the virus to varying degrees. The Public Health Service, America, uses a vaccine beginning with cord of the eighth day and proceeding rapidly to those of the third, second and first day. Vaccines containing the virus in the dead state have been prepared. It gives equally successful results and is now largely used. In Semple's vaccine the virus is killed with 1 per cent. phenol; in Remlinger's method the virus is killed with ether; in Fermi's sero-vaccination treatment, a 5 per cent. suspension of fixed living virus is exposed to 1 per cent. phenol for 1 to 10 days and this vaccine and an immune serum prepared from horses are mixed in varying proportions and injected twice daily. The general opinion is that there is not much difference in the protecting power of the various methods provided a good strain of fixed virus is used. Stuart and Krikorian (1932) made a comparison of the protective power of treatment by living fixed virus, carbolized virus and etherized virus on groups of animals, and the results did not indicate the superiority of one method over the other. In view of such facts much work is now being carried on, both in India and elsewhere, to find out the best methods of producing an antigen that will give the maximum therapeutic effect.

The vaccine in use in the Pasteur Institute, Calcutta, is Semple's carbolized vaccine made from sheep which have died of fixed virus infection. The vaccine consists of a one per cent. emulsion of brain tissue in 0.5 per cent. carbolized saline solution. This vaccine should be used in all cases that have been bitten by a rabid or a suspected rabid animal and also for those cases which have been licked by a rabid or suspected rabid animal on any fresh cuts or abrasions. It is useless to start this treatment when the symptoms have once developed, but if begun during the first week of infection the chances of failure are least. In this Institute, the results of treatment with this vaccine seem to be fairly satisfactory. Out of a total of 10,058 cases during the year 1932, 7,532 were given a full course of treatment, 1,631 were given advice

only as no treatment was considered necessary, and in the remainder the treatment could not be continued. The statistical table during the year shows a failure rate of only 0.38 per cent. and a total death-rate of 0.68 per cent.

For bites, the usual dosage is 5 c.cm. of the vaccine for fourteen days daily, and for licks, 5 c.cm. for seven days. The vaccine is injected into the loose subcutaneous tissue of the abdomen; the whole dose of 5 c.cm. is given in two places, *i.e.*, half the dose (2.5 c.cm.) being injected on either side of the middle line. In the great majority of cases no untoward effects are seen, but a local reaction at the site of the inoculation may be expected to develop during the second week of the course. This is best treated by local application of hot fomentations or the applications of a hot water bottle, and if the reaction is severe calcium lactate may be given.

The untoward symptoms met with are mild neuritis and sometimes acute ascending paralysis. This post-vaccinal paralysis may appear at any time during the course of treatment or some time after the completion of the course; most patients recover spontaneously.

Pregnancy is not a contraindication to treatment. Certain precautions are however to be observed in persons undergoing treatment; they must avoid alcohol and refrain from strenuous exercises such as dancing, tennis, riding, etc. Subjects of malarial fever in the tropics should take a daily dose of quinine. These precautions have to be observed during the course of treatment and continued for at least 10 days after the completion of the course.

Treatment. The treatment is merely symptomatic to relieve the suffering of the patient as there is no drug known which can cure the condition. When symptoms have set in the patient should be removed to a dark room and protected from all disturbing influences, such as draughts of air, sharp noises and light. The diet should be liquid; dysphagia is always marked and recourse has to be had to nutrient enemata. To control the paroxysm, hypodermic injections of morphine or hyoscine may be given; milder antispasmodics are of no avail. Inhalations of

chloroform give more relief than many antispasmodic drugs. Forcible restraint during the paroxysms is often required.

Antirabic serum. Antirabic serum has not proved successful in the treatment of rabies in man. In animal experiments, after removal of cerebrospinal fluid by occipital puncture and introduction of rabicidal serum by the same route, success seems to have been obtained. King (1932) suggests the combination of antirabic serum along with chloroform on the analogy that chloroform is said to have the effect of promoting the action of antitetanic serum by weakening the hold of the toxins on the lipoids of the nerve cells and thus facilitating the combination between toxin and antitoxin. It is yet in the experimental stage.

LYMPHOGRANULOMA INGUINALE, CLIMATIC BUBO AND ALLIED CONDITIONS ; GRANULOMA VENEREUM

Lymphogranuloma inguinale and climatic bubo. These are now recognised to be caused by an identical ultramicroscopic filtrable virus and are nearly always communicated venereally. Minute ulcers develop on the penis, 3 or 4 weeks after exposure to infection, usually in uncircumcised subjects, followed by involvement of inguinal glands.

Much light has been thrown by the observation and experimental work of recent years on the nature of the two diseases, lymphogranuloma inguinale and climatic bubo. Hellerstrom and Wassen (1930) showed that an ultramicroscopic virus existed in the gland pulp and pus of the inguinal bubo which could be passaged in monkeys by intracerebral inoculation. The subsequent experimental work of Hellerstrom, Levaditi and Pindlay added considerable knowledge with regard to the virus.

The consensus of opinion at the present time is that not only lymphogranuloma inguinale and climatic bubo but the conditions known as chronic elephantiasis and ulceration of the vulva, esthiomene, the genito-ano-rectal syndrome and inflammatory stricture of the rectum, are infections caused by the same specific ultramicroscopic virus. Stannus (1933) states that all the different names so long given to this disease describe only regional syndromes of a single infection, and he proposes, for want of a better nomenclature, to describe them as the sixth venereal disease. Such terms as poradenitis, poro-lymphitis, poradenolymphitis, etc., have also been suggested depending on the nature of the lesion, but there is as yet no commonly accepted term.

The virus is present in the affected glands in man and in the sterile pus aspirated from a bubo. It can be transmitted to a number of experimental animals. Monkeys are highly susceptible to intracerebral inoculation developing symptoms of meningo-encephalitis after an incubation period of 4 to 22 days. The virus becomes generalised and can be demonstrated in the blood, liver, spleen, kidneys, lymphatic glands. After inoculation on the prepuce and in the groin, a typical inguinal bubo develops. Guinea-pigs can be infected by groin inoculation with the formation of buboes. In mice intracerebral inoculation produces meningo-encephalitis but local inoculation fails to produce buboes. In man also Levaditi has shown that preputial inoculation produces a typical inguinal bubo. The contagion is usually communicated venereally, but extragenital lesions have also been described, e.g., on the fingers of surgeons or, in young children. In the male a small papular, nodular or more commonly a herpetiform primary lesion is situated in the coronal sulcus. Generally multiple foci of suppuration in the inguinal region occur but a single big abscess may develop. The possibility of co-existing infections, such as syphilis, chancroid, or gonorrhoea must not be lost sight of.

At one time climatic bubo was supposed to be confined to the male sex alone but this has been shown to be erroneous. In the females the primary lesions occur in the posterior part of the vulva or most commonly within the lower third of the posterior wall of the vagina. The greatest brunt of the infection therefore falls on the intrapelvic glands, i.e., the glands lying in the recto-vaginal septum, the ano-rectal or pararectal glands. If suppurative changes are not marked periadenitis and infiltration of the connective tissues occur which fix the uterus to the surrounding structures. In other cases the lymph glands undergo softening, fistulas develop which open into the vagina, rectum or skin surface around the anus. When the infection becomes chronic it spreads to successive groups of pelvic glands with the production of extensive lymph blocking; it also spreads by a retrograde lymphangitis into the connective tissues and organs whose lymph drains to these glands. At the same time due to the presence of the virus, a specific inflammatory reaction develops all round the area. Thus are produced several conditions which are included under the term genito-ano-rectal syndrome or esthiomene. If the reaction is limited to the para-rectal tissues, inflammatory stricture of the rectum is the prominent sign, if on the vulva, elephantiasis of the vulva develops, or the lesion may be more extensive with the production of the whole genito-ano-rectal syndrome.

Ehrlich's reaction has proved of great value for the diagnosis of cases of lymphogranuloma inguinale or climatic bubo. The test is done by intradermal injection of a suspension of pus or gland pulp from an accepted case of lymphogranuloma inguinale, the material should be

heated to 60°C. on two consecutive days and then kept at a low temperature; an intracutaneous injection of 0.1 c.cm. is followed by a local inflammatory reaction with a central zone of necrosis in 48 hours in positive cases. Lymphogranuloma inguinale antigens give positive reactions in cases of climatic bubo and conversely the skin of a lymphogranuloma patient reacts to an antigen prepared from a case of climatic bubo.

Granuloma venereum. Granuloma venereum or granuloma inguinale, though not of established ætiology, is conveniently discussed here as the symptomatology and treatment bear a close resemblance to certain virus diseases. It is a chronic, infectious, ulcerative process of unknown ætiology usually involving the genitalia or neighbouring parts and showing no tendency towards spontaneous healing. The disease is common among young negroes and is widespread in tropical climates. Most of the cases recorded are believed to be due to extension from a primary genital sore though extragenital ulceration has also been noticed. In India the disease seems to be confined to the eastern side of the peninsula. In the hospitals of the Madras city and Vizagapatam a considerable number of cases are treated. On the other hand, the disease has been rarely encountered in the large skin outpatient department of the Calcutta School of Tropical Medicine, and a few cases have so far been reported from other parts of India.

Donovan (1905) first described a short bacillus as the causative organism of granuloma inguinale. It was found in all parts of the ulcers but was particularly abundant in the deeper ones, where all other organisms were absent. These 'Donovan bodies' were at first believed to be protozoa but are now regarded as probably of bacterial nature. Though the ætiology of the disease is still uncertain the Donovan bodies are such a constant histological finding in the typical ulcer that one is justified in expecting their demonstration in every case. This micro-organism (though the suggestion has been put forward that it is a cell inclusion body, *i.e.*, evidence of cellular reaction to an unidentified virus) plays a part in the ætiology of the disease, but there is, however, no satisfactory evidence that it is the primary invading organism or that it is the only organism maintaining the specific nature of the lesion. McIntosh (1926) was successful in transmitting the disease from one individual to another and constantly found the presence of Donovan bodies in the experimental lesion. Campbell (1928) on the other hand, contests the view of McIntosh and argues that in the transplanted tissues other organisms might be present, and he was unable to transmit

the disease by inoculation of the culture into laboratory animals or human beings, including himself.

Treatment. *Lymphogranuloma inguinale.* The patient should be put to bed early and kept on a nutritious diet. If the glands suppurate aseptic aspiration is indicated, excision of the glands is not advisable in these cases as secondary infection may occur. Chemotherapy has not proved successful. Solganal has been used in doses of 0.1 to 0.2 gm. intravenously every second day, and satisfactory results are obtained after two to six weeks' treatment. Lohe and Rosenfeld (1932) obtained good results by intragluteal injection of an oily suspension of solganal in doses of 0.2, 0.3 up to 0.6 c.cm. of 2 to 20 per cent. twice weekly. A series of 20 injections with a total of $1\frac{1}{2}$ gm. of the gold salt is usually necessary. In case of kidney disease or dermatitis and when gold is contra-indicated, vaccine treatment combined with local application of X-rays gives satisfactory results. Good results are also reported from intravenous injections of such antimony preparations such as neostibosan, fouadin, stibenyl and tartar emetic. Intramuscular injection of serum from convalescent patients has also been tried. It is given in doses of 5 c.cm. every day and a total of about 50 to 100 c.cm. of serum may be given.

Protein shock treatment by intravenous injections of T.A.B. vaccine, in doses gradually increased from 100 to 500 million organisms, at four or five days' intervals, has given good results. Recovery has been reported by daily intravenous injections of 0.03 to 0.1 gm. of methylene blue in 1 per cent. solution. Vaccines made from infected glands have been tried. Frei's antigen has been reported favourably in doses of 0.2 c.cm. gradually increased to 1.6 c.cm. at 2 to 4 days' intervals.

Granuloma venereum. As there are no constitutional symptoms, no particular care is necessary as regards the management of the patient. If there is anaemia iron and arsenic along with the specific treatment are indicated. If there is ulceration an ointment containing 1 per cent. antimony has been advocated, but this treatment is very painful and does not seem to have any effect on the ulceration. Surgical treatment was much practised in earlier days. Excision of the lesion

along with a considerable portion of the healthy tissue, with or without cauterization, may give some amount of success. Irradiation by X-rays has also been tried but has proved unsatisfactory.

Specific treatment. Intravenous injection of tartar emetic was first introduced in 1913 by Aragao and Vianna, and very successful results were obtained with it. In Dutch Guinea de Vogel (1907) found that the results of antimony treatment of granuloma inguinale were very encouraging; in a total of 5,736 cases, 86.1 per cent. were cured after one series of injections and 12.8 per cent. after a second series. Numerous other workers have obtained similar results. Manson-Bahr and Anderson (1927) have estimated the total amount of antimony necessary for a complete cure, which varies from case to case, and is roughly between 17.5 to 17.9 gr. Though tartar emetic is considered almost a specific for the disease, the results obtained have not been uniform. In the early cases complete cure is possible and recurrences are rare, but in the advanced type of case, improvement is not satisfactory and relapses are frequent.

The actual dosage has varied with different workers. In the majority of cases it is well to begin with a dose of 2 c.cm. of 1 per cent. solution of tartar emetic, gradually increasing the dosage to 5 to 10 c.cm. at daily intervals. This may be sufficient to cure a case, but in very extensive and long-standing cases a larger number of injections may be necessary. In chronic cases two or three courses may have to be given at two or three weeks' interval. Having once begun the injections, the treatment should be continued. As is usual with antimony compounds, untoward effects have been observed. Coughing fits during or immediately after the injection and pain in the joints are signs of intolerance to the drug. Jaundice has also been observed.

In order to obviate the toxic symptoms that are observed after the intravenous injections of tartar emetic, other antimony preparations have been employed. Antimony sodium thioglycollate is given to patients who cannot tolerate tartar emetic.

The dose is 0.05 to 0.1 gm., dissolved in 10 to 20 c.cm. of sterile water every third or fourth day until 15 to 25 injections are given. Intravenous or intramuscular injections of triamide of antimony thioglycollic acid have been tried.

Recently the pentavalent compounds of antimony have been tried. Manson-Bahr is of opinion that stibosan (von Heyden 471) is more efficacious than tartar emetic. Giglioli (1928) used stibenyl with good results. The initial dose is 0.1 gm. increased by 0.1 gm. to 0.6 gm. in 20 c.cm. of sterile saline injected intravenously. It is said to be effective in cases resistant to tartar emetic and toxic reactions have been rarely encountered.

Fouadin, a trivalent compound of antimony, has lately been employed. Williamson and others (1933) consider it superior to the pentavalent compounds. The drug is available in ready-made stabilised solution and is given intramuscularly, and even subcutaneous injections are followed by very negligible local reactions. The initial dose is 1.5 c.cm. gradually increased to 5 c.cm. every day or every alternate day and a total of 40 to 60 c.cm. constitutes a course. In a certain percentage of chronic cases the condition does not improve with antimony treatment, but remains stationary. These cases may be due to development of antimony-fastness, similar probably to arsenic-fastness in syphilis. Such cases may react to non-specific protein therapy, and protein shock treatment by T. A. B. vaccine with antimony may prove effective.

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PART V

REMEDIES USED AGAINST MISCELLANEOUS TROPICAL DISEASES

CHAPTER I

NUTRITIONAL DISORDERS

BERIBERI

The term 'beriberi' has been applied to a condition of peripheral neuritis, occurring principally among rice-eating populations in the East. While it manifests itself in many forms, it can be classified into two well-marked types :

(a) *The dry type*, characterised clinically by great wasting, anæsthesia of the skin, finally resulting in paralysis of the limbs.

(b) *The wet type*, in which the most marked symptom is excessive oedema which may affect the trunk, limbs and extremities. In these cases the heart usually becomes enlarged and death may result suddenly from heart failure. In this type the mortality is high.

Beriberi is a vitamin B deficiency disease associated with the over-milling of rice. The incidence of beriberi in the Japanese navy in 1912 was 1 per 1,000 while in 1919 to 1921, the figure rose to over 4 per 1,000. This was apparently due to an increase in the white rice ration which was later reduced with beneficial results. When the issue of unpolished rice to the Dutch East Indian Army was stopped the incidence of beriberi rose from 1.8 per 1,000 in 1918 to 26 per 1,000 in the first eight months of 1922. In the Infantile Beriberi Hospital in Manila the admission rate fell from 7.29 per cent. in 1915 to 0.45 per cent. in 1927, and this improvement was due to the issue of *tikitiki* extract (made from the pericarpal layer of rice grain) on a large scale to the poorer classes. The recommendation of the Far Eastern Association of Tropical Medicine Congresses in 1923 and 1925 clearly support the vitamin

deficiency theory. McCarrison is not satisfied that vitamin deficiency is the sole agent in the causation of beriberi. He holds the view that two factors are in operation in the causation of beriberi:—(i) A nutritional or intrinsic, factor; and (ii) an unknown extrinsic factor peculiar to certain tracts of country or to certain individuals. As regards the first factor he finds that it is rice relatively less deficient rather than relatively more deficient in vitamin B which is responsible for the human disease. Graham (1927) stated that supposing the figure 100 represents the amount of vitamin B necessary to keep pigeons in health on any given diet, then true beriberi will occur at figures 75 to 90 while a figure of 50, or lower, will cause *polyneuritis columbarum*. This condition is however quite distinct from true beriberi in pigeons. In the former the heart is atrophied, while in the latter cardiac hypertrophy and degeneration are present. The condition of the heart is considered to be the essential distinguishing feature. The extrinsic toxic factor is of metabolic origin, but a considerable amount of research has been carried out on the possible association of a micro-organism with beriberi. Bernard claims that beriberi is an acute febrile illness and that peripheral neuritis, with or without oedema, only occurs later in the cases that survive. Bernard (1931) isolated *B. asthenogenes* which he claims to be an important ætiological factor. Animal experiments, complement fixation tests, etc., support this view but two additional ætiological factors are demanded, *viz.*, a gastrointestinal condition favouring the action of the organisms and a lowered resistance resulting from faulty diet. If one of these factors is absent, even though the other two are present, beriberi does not result.

Bernard's view regarding the toxic infection and faulty diet has been supported by other workers and some have also associated endocrine disturbance. Matsumura (1927) described a 'beriberi bacillus' resembling *Bact. coli communior* which was isolated from the intestines in experimental animals and from the faeces in 74 per cent. of human sufferers. Positive agglutination tests were obtained. It was claimed that the bacillus is the principal ætiological factor in experimental beriberi. The

possibility of there being a toxin in rice itself has received little consideration. Ohmori (1917) attempted to prove that cold alcoholic extract of rice contains a toxic substance, while Acton and Chopra (1925) have shown that damaged rice may be classified as 'epidemic dropsy rice' and 'beriberi rice' according to whether the water-soluble toxin or the alcohol-soluble toxin predominate. Braddon considered that beriberi is mainly caused by a toxic substance which develops in stale rice as a result of fungus growth. The fungus acts from the exterior of the grain inwards, in a similar manner to the ergot of rye. Van Dieren (1907) draws attention to the fact that the symptoms of beriberi resemble pellagra, ergotism and lathyrism and suggests grain intoxication as the cause. More recently, Teru Uchi and his collaborators have advanced evidence of the presence of 'oryza toxin' in rice. These workers describe the results of certain experiments carried out on pigeons, fowls, dogs, rabbits, monkeys and also 4 men, which are claimed to prove the existence of rice toxin. Simpson (1934) however could not confirm this work. The consensus of opinion appears to be that beriberi is associated with vitamin B deficiency, but that another factor, probably of a toxic nature, is also present.

The water-retention theory was first put forward in 1928 by Mebius and Wenckebach who showed that oedema occurs in heart muscle, chiefly intracellular in site. Excess of water interferes with the normal fluid exchange and consequently with the contractility of the myocardium. The presence of vitamin B controls the osmotic pressure and its absence leads to water retention. It is considered by some that disturbance of lipid metabolism is responsible for the symptoms of the disease. Findlay suggested that the enlargement of the cortex of the supra-renals in beriberi results from an increased storage of phosphorised lipoids, which can only be used by the nucleus of the nerve cell in the presence of vitamin B, so nerve degenerations ensue. Langen concluded that the symptoms of beriberi are the consequence of a disturbance of the lipid metabolism, and this is due to lack of a substance necessary for the synthesis of the phosphatides, namely vitamin. Kimura showed that the nerve changes are degenerative and

not inflammatory ; they commence in the axis cylinders and in acute cases primary injury to the central nervous system may occur. Honda found less affection of the vagus and sympathetic nerves than of spinal nerves. The heart undergoes fatty degeneration.

Infantile beriberi has drawn a good deal of attention in the literature during recent years. The importance of this subject can be realised from the fact that in the Philippines 16,500 deaths occur annually from this cause (about 28 per cent. of total deaths among infants under 1 year). Most of the cases occur in breast-fed infants but exceptions are recorded. It is maintained by some that the mothers of such infants are themselves sufferers from beriberi but according to others in 25 per cent. of cases no symptoms or signs of the disease could be detected in the mother. Clinically, the picture resembles the adult type with œdema and cardiac failure but apparently neuritis (except for that of the laryngeal nerves, causing aphonia) is usually absent.

The most important advances in the clinical study of beriberi are undoubtedly those dealing with cardiology. In 1928 Wenckebach gave a full description of the heart in beriberi. From the onset of the disease the right side of the heart is enlarged and the same is true of the left side but to a lesser extent. The increase in the size of the heart chiefly on the right side progresses rapidly with cardiac failure. Aalsmeer (1931) described what is now known as the 'adrenalin effect', viz., a marked fall in the diastolic blood pressure (practically to zero) after the injection of adrenalin in beriberi patients. This fact is a useful diagnostic criterion.

Prophylaxis and treatment. There is no doubt that the eating of polished rice is a factor of greatest importance in the causation of beriberi ; one would naturally think that the disease could be quickly and easily stamped out by similarly supplementing the diet with food rich in vitamins or by consuming only unpolished rice. This is not always possible.

The difficulty of supplying a sufficient quantity of vitamins in a palatable form to a rice-eating population, if only polished rice is available, is also great. Jansen and Donath (1926) isolated

pure vitamin B from rice bran. They found that one part of this substance in 500,000 parts of washed polished rice protects *Munia maja* (a finch) against polyneuritis. Clinically, beriberi has been treated with this product with striking results. The excellent results obtained in Philippines from the administration of *tikiliki* extract have already been mentioned. The preparation is an alcoholic extract made from the pericarpal layer of rice grain and it is issued by the Public Welfare Board in large amounts. The dosage is as follows: To mothers, in addition to a balanced diet, a tablespoonful of the extract is given after meals; for babies 3 to 4 teaspoonfuls are sufficient in mild cases, but in severe cases 5 to 7 teaspoonfuls are required. Work on similar lines has been done in the Dutch East Indies. Here the public health authorities issue rice-husk vitamin in four forms: (1) Tablets, each containing 7.5 gm. of rice husk absorbed by kaolin; 1 to 3 tablets a day protect an adult eating completely decorticated rice, while for treatment 8 to 12 tablets daily are necessary. (2) A powder similar to the tablets. (3) Extract of antiberiberi vitamin. A daily dose of 1 to 10 c.cm. is sufficient for adult protection. (4) Ampoules (2 c.cm. each) containing 1 mgm. of vitamin which is the daily adult dose. Later, it was found that the above dosage had to be increased somewhat, but toxic effects may sometimes follow the injections. Satisfactory results have also been obtained from the use of various 'oryzanin' preparations and from Wenckebach's 'eviunis.' The substitution of diets containing sufficient amount of vitamin B, in place of those lacking in it, is practised as a preventive as well as curative in not too advanced cases. Vedder (1916) recommended for this purpose the use of beans, peas and other legumes at least once a week together with fresh vegetables and fruits. White potatoes and fresh meat should be given at least once a week but preferably daily. Findlay advised the use of yeast, which contains a large amount of vitamin B. This is now available in the form of marmite, which can be added to soups, etc. Sudley advises 100 to 150 gm. of fresh palm oil daily in mild cases as an effective measure, and also in severe cases if combined with the use of red rice and fresh

mealies. Ogata obtained good results from soya beans as a protection against beriberi.

Various drugs have been tried. Urotropine has been claimed as a specific in doses of 7.5 gr., 4 times a day, for 15 to 21 days. Others have obtained good results with Lugol's iodine solution when a vitamin-rich diet has failed. The similarity between the adrenalin effect in Basedow's disease and beriberi has suggested the presence of thyroid dysfunction. In the treatment of sudden heart failure the usual cardiac tonics fail, and adrenalin is definitely harmful since it causes a marked drop in the diastolic blood pressure, already low in beriberi, and an increase in the venous pressure. According to Wenckebach pitressin raises the diastolic blood pressure in beriberi from almost zero to 75 to 90 mm. and the venous pressure suddenly falls. This beneficial effect may last from 25 minutes to 1½ hours. On the other hand other observers have found that pitressin is not always successful, because the relief of the right heart may throw a sudden burden on the left heart with fatal results. Venesection is an important and a valuable aid in the relief of cardiac failure in beriberi.

EPIDEMIC DROPSY

Rice-eating people are prone to suffer from a condition of œdema which is frequently epidemic and not connected with the usual cardio-renal causes. It was pointed out by Megaw that the condition in one extreme presents the syndrome of epidemic dropsy (fever, rash, gastro-intestinal symptoms, capillary dilatation, glaucoma, etc.) and at the other extreme the picture of chronic beriberi with peripheral neuritis. While there may be some resemblance between the two, epidemic dropsy is now considered as a distinct and separate clinical entity.

The dry or paraplegic form of beriberi is associated with peripheral neuritis with early loss of knee jerks. The patient is emaciated and ataxic and the calf muscles are extremely tender and wasted. It is not possible to confuse these cases with epidemic dropsy. But in the wet form of beriberi in which the

patient is swollen all over and the symptoms of paraplegia are not well marked the two diseases resemble one another and sometimes difficulty arises in differentiating the two conditions. In fact the occurrence of this wet form of beriberi led to the belief that epidemic dropsy is nothing but a form of wet beriberi. The distinctive features are that in epidemic dropsy there are no symptoms of peripheral neuritis excepting pains and aches in the muscles especially of the calves. Fever is usually present which is seldom present in beriberi. Gastro-intestinal irritation, indigestion and diarrhoea which are very common in epidemic dropsy are not encountered in beriberi. The erythematous rash and vascular nodules (sarcoids) are characteristic features of epidemic dropsy. Common complications like glaucoma, abortions, hæmorrhages, etc., of epidemic dropsy are not seen in beriberi. Sucklings are affected in beriberi, but infantile epidemic dropsy is unknown.

According to Mazumdar (1933) epidemic dropsy appeared first in Calcutta in the year 1877. It appeared again in 1878 and 1879 the outbreak being limited to certain quarters of the city and the death rate was high. A small outbreak in a few houses only occurred in Calcutta in 1901. No further cases were reported, till the outbreak in 1907. The feature of this outbreak was said to be the presence of neuritis, deep-seated pains in the feet and legs were generally present and distinct tenderness of the calf muscles was present in a fair proportion of cases. The essential symptom was oedema of the lower extremities, the upper extremities and the trunk being subsequently affected in severe cases. The fever was mild, seldom exceeding 101°F.; cardiac disturbances (palpitation, irregularity of the heart beat, rapidity of the pulse and murmurs) were numerous; anæsthesia of the skin was noticed in this outbreak; weakness and unsteadiness of gait and slight paralysis of the limbs with subsequent wasting of the muscles was also met with in severe cases; the knee jerks were impaired or lost in many instances. Fifteen deaths were recorded out of about 300 cases, there being a mortality of 5 per cent. Death was brought about sometimes suddenly and sometimes slowly. All ages and both sexes, the weak as well as the strong, the well-to-do along with the poor were equally attacked. The outbreak continued throughout the cold weather in 1907-08 but gradually subsided. The next epidemic was in 1909 and after that epidemics occurred in 1919, 1927, 1930, 1931-32 and 1934. The epidemic usually starts in the beginning of August and goes on through September and October and sometimes November and December. It has been observed that this syndrome shows a peculiar periodicity. In certain

years, a widespread epidemic is met with, followed by a quiet period. These waves of morbidity are difficult to explain. Each epidemic brings forth its own peculiarities and cases of one year greatly differ in severity, signs and symptoms from those of another year. The morbidity rate as well as the incidence of mortality vary enormously. In some epidemics the death-rate is very high while in others it is exceedingly low. Although all members of a family are on exactly the same diet, the severity of symptoms varies enormously in different individuals. Children under five and persons over fifty either escape entirely or are only slightly affected.

Ætiology. Epidemic dropsy, unlike beriberi, is not associated with vitamin deficiency but rather with a toxic factor found among the rice-eating people and having its origin in rice grain which has been stored under unsatisfactory conditions. In the presence of excessive heat and moisture such rice becomes diseased and develops toxic products. All cases of epidemic dropsy seen by the author occurred among those whose main dietary consisted of rice and in almost every case it was established that the rice was diseased. A spore-forming proteolytic bacillus of the *vulgatus* group is commonly found in the diseased grain. In this connection it may be mentioned that Bernard of Saigon found a very similar bacillus and described an infection occurring in animals when fed on these bacilli. There is no close connection between avitaminosis and this disease, because if this were the case it would occur in an epidemic form when associated with famine conditions and this certainly has not been so in Bengal. The findings of Acton and Chopra (1927) regarding this bacillus occurring in the urine and stools of patients have been lately confirmed in many cases. Rice in the form in which it is harvested is enclosed in a tough indigestible husk before it is husked. In this condition it is protected from the attacks of microbes and moisture, but when stored under unhygienic conditions and exposed to excessive moisture and heat it is liable to deteriorate. The poisons are most readily formed in rice grains which after having been deprived of their vitality by parboiling and of most of their aleurone and other protections by excessive milling, are then badly stored in a humid and warm atmosphere. In such conditions they are attacked and damaged by fungi and bacteria, and particularly by a strongly proteolytic bacillus of the *vulgatus* group.

Some of the toxins formed are soluble in water and affect the heart, besides producing a fall of blood pressure, bronchial constriction and swelling of the limbs, experimentally. Some are soluble in alcohol, which act as neurotoxins and have no effect on the respiration or blood pressure. Respective amount of water-soluble and alcohol-soluble bases differ in different grades of rice. Those in which water-soluble toxins predominate are termed epidemic dropsy rice and those in which alcohol-soluble ones predominate, beriberi rice.

Rice test. The test for diseased rice introduced by Acton and Chopra is very simple. Dry grains from the suspected supply are soaked in water (or glycerine) in a petri dish laid on a black surface. Healthy rice is translucent; the diseased rice shows areas of white opacity and softening, usually starting at the embryonic site. The proportion of grains which show such degeneration determines the degree of infection in the rice. When the grains are badly diseased, the rice can be crushed up into a powder by the fingers. It is, however, necessary to differentiate such grains from the barrows of the larvæ of weevils. Section of diseased grains shows a liquifaction of starch cells.

Signs and symptoms. Dyspnoea is an early feature, complained of before gross evidence of the cardiac damage appears. Oedema occurs to a greater or lesser extent in all cases. Anæmia is a prominent feature in all cases. The blood pressure is generally low and the pulse compressible, probably due to widespread dilatation of the capillaries causing oedema of the heart muscle. The condition of the heart can be classified into three groups: (a) *Acute or fulminating*: in which the patient has the heart affected from the very start, failure progresses and death may occur within four to seven days. These cases resemble the picture of an acute left-heart failure. This type, with a high mortality, was common in the epidemics of 1926 and 1927. (b) *Subacute or chronic*: here the heart is less rapidly affected, and failure, from which recovery is usual, is a slow process. These cases resemble the picture of a combined right and left-sided failure, with slight cyanosis, jugular distension and general systemic venous congestion. This occurred in the 1932 epidemic. (c) *Formes frustes*: here the heart either wholly escapes, or is very slightly affected. This type was seen in one or two epidemics. The existence of these three distinct types cannot be explained in terms of the varying degrees of histological changes in the heart wall itself. But it is easy to understand the mechanism of these three modes of cardiac failure, by recalling the picture of a general capillary dilatation. The degree and severity of circulatory failure along with a secondary cardiac weakness are directly proportionate to the degree and extent of capillary dilatation that exist. The acute fulminating type of failure starts with a very deep and extensive capillary distension and stasis, somewhat similar to that in surgical shock or acute histamine poisoning. The blood is locked up in the capillaries, and thus is side-tracked from the circulation. Consequently the veins, the heart and big arteries are relatively empty, and sudden syncope and death may result. On the skin an erythematous rash is frequently met with which may be associated with the formation of sarcoids here and there. There may be pigmentation of the face and extremities.

While cardiac involvement is the rule, its severity is not uniform. In certain epidemics, severe diarrhoea is the predominant symptom and the cardiovascular symptoms are of a mild nature. In patients with constipation, the cardiac features usually progress rapidly and

become serious, often leading to a fatal end. In yet another group, mild cardiovascular symptoms are associated with a high rate of ocular complications such as glaucoma ; there is as a rule only slight diarrhoea and cedema of the legs in these patients. Diarrhoea is probably produced by the toxic bases in the intestines which not only damage the capillaries and produce cedema, but also produce exfoliation of the mucous lining of the gut.

The intoxication starts with the ingestion of the affected rice. In the stomach and duodenum local irritation is produced which may proceed down to the rectum, causing areas of congestion and necrosis of the mucosa. Local injury to the rectal mucosa causes occasional vascular swellings which bleed profusely. The absorption presumably takes place through the liver which also shows the typical lesions and the antitoxic function of the liver is severely tested but fails, and finally the toxin reaches the general circulation. Although symptoms may commence as early as twenty-four hours after feeding, the effects of this intoxication are very severe and serious and may continue for some weeks after a rigid stoppage of the suspected food-stuff. This suggests a massive storage of the toxins, or a linkage with the cells of various tissues, such as is known to occur in heavy-metal poisoning, with lead or mercury, for example.

Treatment. Rational therapy might be summed up as follows:—

1. Stimulate elimination of the toxins by the bowels.
2. Neutralize or break down the toxins in the bowels into inert harmless products.
3. Prevent absorption of the toxin.
4. Stimulate the antitoxic power of the liver so that the toxins are broken down into simpler products.
5. Stimulate the defensive mechanism of the body whereby the ductless glands may produce hormones destructive to the toxins.
6. Quicken up the process of elimination by the kidneys.
7. Add to the diet appropriate vitamins which may render the toxins inert.
8. Counteract the 'capillary crisis' throughout the body and thus hasten the process of circulation.
9. Support the heart by tonics.
10. Relieve the venous congestion by leeches or venesection.

In practice, however, all these ten points cannot be dealt with for want of exact knowledge, but the prospect is far more hopeful than might at first sight appear. We have, in the past, relied exclusively on cardiac tonics, in one shape or another, and have ignored the other vital therapeutic points. Since the heart is 'sinned against as well as sinning' this narrow view of therapy could not possibly give the best results. The 'cardio-capillary crisis' is best dealt with by that group of drugs which has a sustained vaso-pressor effect, combined with the power to counteract the increasing permeability of the capillary walls. It is fortunate that in ephedrine we possess a potent remedy whose selective seat of action is in the capillaries, and an extended use of ephedrine has fully confirmed the success. The digitalis group of drugs has failed, because this capillary crisis is left untouched and until this is corrected no cardiac tonic can maintain adequately the circulatory process. In calcium we possess a means of decreasing the permeability of the capillary walls.

Rice is entirely cut out from the dietary. It is definitely established that the progress is much slower if rice is allowed as a part of the diet. Diarrhoea, if mild, needs no treatment, but if severe 15 to 30 min. of liquor ferri perchloridi with a little glycerine are distinctly helpful; liq. strychnine hydrochlor. may be added when there is weakness of the heart. Apart from the astringent action of iron on the gut it also acts on the hæmopoietic system and stimulates blood formation. In cases where the heart is involved and there is decompensation, digitalis gives unsatisfactory results. Injections of small doses of adrenalin, such as 3 to 4 min., give only temporary relief in some cases and ephedrine by itself fares no better.

The drug which is most effective in controlling the heart symptoms is tincture of ephedra, prepared from an Indian species of ephedra, *E. vulgaris* Rich. (*E. gerardiana* Wall.), first introduced by the author. The Indian variety of ephedra contains larger quantities of pseudo-ephedrine and comparatively less ephedrine as compared with the Chinese varieties. The

vaso-pressor effect is stronger in the case of ephedrine which acts almost entirely on the vasomotor nerve endings, while pseudo-ephedrine has been shown to have some stimulant action on the musculature of the arteries and a similar action on the myocardium. It is this stimulation of the myocardium by pseudo-ephedrine, and the stimulation of the accelerator mechanism by ephedrine which makes tincture of Indian ephedra a very valuable remedy when the heart is failing. Digitalis is not only ineffective but may be distinctly harmful especially in the early stages. When œdema of the lungs sets in it is better to perform venesection and let out 10 to 12 oz. of blood, so as to relieve the over-loaded right heart and stagnant pulmonary circulation.

PELLAGRA

Pellagra is an endemic disease characterised by dermatitis and pigmentation of the skin especially of the exposed parts of the body, marked emaciation and certain nervous manifestations. The eruption consists of symmetrical patches of erythema on the back of hands, forearms, and extending up to the neck.

It is well known that pellagra is a disease of the poor in rural districts subsisting on limited choice of food. It has been shown to be associated with the use of maize as a staple article of diet, while its occurrence in populations who subsist on wheat or rice is comparatively rare. The above facts throw some light on the causation of the disease which may be briefly stated as follows: (i) firstly, it may be due to some factors in the dietary, either a deficiency of vitamins or of certain essential constituents, or to elaboration of toxins; and (ii) secondly, it may be the result of some infectious process. The latest view, however, is that the absence of some essential food factor, whatever its true nature may be, is the principal cause operating in the ætiology of the disease, though an infectious process may be associated with it.

Vitamin deficiency. Just as beriberi and scurvy are now recognised as food deficiency diseases due to the absence of certain essential vitamins in the diet, substantial evidence has been put forward that pellagra belongs to the group of food deficiency diseases. In this connection may be noted the classical work of Goldberger and his co-workers who furnished some evidence in favour of the food deficiency theory and showed that there is absence of a pellagra-preventive factor (P. P.) in the diet of people suffering from the disease.

Among the earlier workers, Deeks (1912) and later Funk suggested that pellagra is produced by certain deficiencies in the diet. Goldberger and his associates (1914) conducted experiments on eleven prisoners by giving them rich carbohydrate diet with deficiency of protein elements. The diet consisted of highly milled wheat flour, maize meal, corn starch, white rice, cane sugar, etc. After about six months, six of them developed symptoms identical with pellagra, but in a control series of experiments with normal diet none developed the disease. Later (1925) the existence of a hitherto unrecognised factor necessary in the diet to prevent or cure pellagra was announced. It was shown that yeast and other articles of diet which are known to contain vitamin B, contain in addition to the antineuritic heat-labile vitamin B another water-soluble complex, *i.e.*, the P. P. factor or pellagra-preventive factor. Chick and Roscoe (1927) showed that vitamin B is not a single factor but consists of two parts, B₁ and B₂, the absence of B₁ causes beriberi while deficiency of B₂ produces ophthalmia and dermatitis.

The richest sources of vitamin B₂ are yeast and yeast extracts, liver, eggs, milk, meat, and green vegetables, while fruits, legumes and cereals are relatively poor. Vitamin B₂ has thus a distribution in food-stuffs somewhat similar to that of antineuritic vitamin B. In general the food rich in vitamin B₂ are those containing proteins of high biological value, but its presence in abundance in protein-free extracts made from yeast, egg white and liver is proof of its separate existence apart from the proteins with which it is associated. Ordinary canned tomatoes are deficient in P. P. factor, but may prevent pellagra if given in sufficient quantity and so also the commercial wheat germ.

Though the P. P. factor is probably present in all the foodstuffs which contain antineuritic vitamin, it is however variable, as certain strains of yeast have been found to be potent sources of anti-pellagra factor though poor in antineuritic vitamin. It has been held that certain processes of preparation eliminate the pellagra-preventing vitamin from the diet. In milling maize the vitamin content of the grain is removed as from analysis of the vitamin content of milled maize it has been found that the P. P. factor is deficient according to the degree of milling. Excessive milling of wheat gets rid of vitamins, and the bread made from highly milled flour is dietetically deficient. Similarly the practice of using alkalis in the preparation of bread is another factor in the food deficiency problem. Others however think that the bacterial or mould diseases of the corn grain are responsible for the destruction of the vitamin contents.

In recent years cases of secondary pellagra have been described, which stress the importance of vitamin in the dietary. Patients suffering from chronic maladies of the digestive tract develop pellagra as a secondary condition, especially alcoholics and those who do not take a well-balanced diet. In these cases the primary digestive disturbances most frequently consist of chronic diarrhoea or diarrhoea alternat-

ing with constipation and accompanied by pellagra dermatitis, stomatitis, etc. These conditions are said to be due to deficient absorption of vitamins as the result of a pre-existing disease of the digestive tract.

In the light of recent studies of the vitamin B₃ content of cereals the theory of vitamin deficiency however breaks down. If pellagra was caused by a simple deficiency of vitamin B₃ it should occur chiefly where people subsist on poor diets containing rice, rather than maize, as the latter has been shown to contain a high proportion of vitamin B₃. But among the rice-eating people, beriberi and not pellagra is the menace, while pellagra is of common occurrence among those whose principle article of consumption is maize

Amino acid deficiency. The association of pellagra with maize consumption has given considerable support to the theory that the disease might be caused by lack of proteins of high biological value. The commission which investigated the occurrence of pellagra among the Turkish prisoners in Egypt during the Great War showed that a certain amount of protein is necessary for rebuilding of tissues. It has been found that the nitrogen contained in certain amino acids is utilised while others do not serve this purpose. In this respect animal protein is superior to maize protein. Forty grammes of animal protein daily are considered as the minimum biological protein value, i.e., the amount necessary to maintain the nitrogenous equilibrium of the body. The protein of a diet is estimated by its assimilable or biological value and not by its gross weight. The biological protein value of any diet can be obtained by dividing the total quantity of a substance by the following factors: for animal protein 1, rice protein 1.27, pulse protein 1.82, wheat flour protein 2.55 and maize protein 3.4. Hence to keep the body in nitrogenous equilibrium with maize protein alone, about 136 gm. of such protein have to be consumed. In the case of Turkish prisoners in Egypt their rations had a biological protein value of 33.5 and hence a large number of cases occurred among them. It has also been suggested that in a susceptible subject the protein requirement may be sufficient while at rest, but during hard labour or during a time when his metabolism is faulty, pellagra may set in.

Goldberger and Tanner (1922) showed that a low protein value of diet was not necessarily associated with the development of pellagra. They found that in the causation of pellagra certain amino acids were deficient in the diet consumed by the patients. The protein of maize flour for instance, zein, is deficient in certain amino acids, such as tryptophane and lysine. Benefit has been reported from the administration of cystine and tryptophane to these patients and in preventing the occurrence of pellagra.

Animal protein as a class contains a more varied assortment of amino acids than vegetable proteins. It is generally true that nitrogenous equilibrium can be maintained on a smaller intake of animal

than of vegetable protein. The good effects on pellagra noticed after the addition of meat, milk and eggs are probably due to a supply of a richer variety of essential amino acids. The theory that pellagra arises as a result of an amino-acid deficiency has led to many investigations with the object of finding out the relative biological values of the proteins of the common foodstuffs. The results of these experiments show that pellagra-preventing foods, such as meat and milk, have high protein values while maize has a low protein value. It is also significant in this connection to note that values obtained for maize proteins by several workers have not been found to be inferior to those of wheat or other cereals. Wilson (1932) examined the B_3 contents of various diets which have been known to be associated with either the causation or cure of pellagra. It is claimed that vitamin B_3 deficiency has no connection with the occurrence of the disease, as it was found that 150 gm. of meat added to a pellagrous diet of sufficient caloric value cured the disease while 210 gm. of maize were unsuccessful in that respect though the vitamin content of both was the same. Pellagra-producing and -preventing diets showed that there is no consistent relation between the vitamin B_3 value of diet and the incidence of the disease. On the other hand definite connections were shown to exist between the protein value of diets and pellagra. This protein value, as has already been mentioned, is dependent upon the amino acid content, and in this respect the vegetable proteins are generally less efficient in maintaining the nitrogen equilibrium than those in meat and other foods.

The action of these amino acids in the prevention and cure of pellagra brings to light some interesting facts. Cystine has been known to promote the growth of vitamin B and is probably connected with oxidative processes and with detoxication of cyanogen compounds. All of these functions appear to be disturbed in pellagra. Hopkins isolated glutathione, a combination of cystine with glutamic acid from yeast, muscle and liver. Cystine is also present in the antipellagra diet recommended by Goldberger, and it seems, therefore, reasonable to think that lack of cystine in the dietary may play a part in the causation of pellagra. In addition the part played by the mineral constituents of the foodstuff, such as iodine, iron, copper, manganese, etc., needs investigation which may throw further light on the subject.

Maize toxin. In spite of many satisfactory theories regarding the aetiology of pellagra, the usual association of the disease with the consumption of maize still remains to be explained. The possible toxic effects of maize, spoiled or unspoiled, have therefore been much discussed. The occurrence of the skin lesions on exposed parts of the body in pellagra led to the idea that maize might contain a photo-sensitizing substance analogous to that contained in buckwheat. Jobling and Arnold (1923) produced experimental evidence that toxic substances are produced in the intestine as a result of a maize diet; on injection of the extract of the material into animals they were found to be sensitive to

light with swelling and oedema of the eyelids. The search for a toxic substance has lately been made.

Mellanby thinks that toxic substances (toxamins) in cereals give rise to pathological conditions that are seen in pellagra and after administration of appropriate vitamins these toxamins can be neutralised. The cutaneous symptoms according to him are due to vitamin B₂ deficiency, which can be remedied by giving such vitamins in the diet, and that the nerve lesions are caused by the presence of toxamine, more especially present in the maize. Roscoe however is not inclined to believe in the existence of any toxamine in maize. Maize contains, weight for weight, the same amount of vitamin B as wheat and more than what rice contains; if maize were definitely toxic then the greater the amount of maize consumed the worse would be the symptoms of pellagra, but it is agreed that the opposite is the case in such instances.

Sabry (1931 and 1932) made an extensive study into the part played by maize toxin in the causation of pellagra. He disapproves of the vitamin deficiency theory and is of opinion that pellagra is due to a toxin which may occur in maize or in any other cereal but always occurs in a specific cereal, namely beans. The toxin of pellagra according to him, is causally related to the hyper-pigmentation that occurs in the disease and he believes it to be a dioxypyhenylalanine. He obtained very satisfactory results with intravenous injections of sodium thiosulphate. The usual procedure was to give intravenously 10 c.cm. of a 10 per cent. solution daily, the number of injections varying from twenty to sixty. Chick (1933) has recently advanced a view which is perhaps a combination of several factors. She postulates that pellagra may be caused by a toxic substance derived from the maize diet which can be corrected by sufficient quantity of protein or perhaps by sufficient vitamin B which is present in these proteins.

Infection theory. Sambon (1905) maintained that pellagra is a protozoal disease, but this has not been confirmed. No satisfactory evidence has been adduced to show that pellagra can in any way be considered a directly infectious disease. Some investigators have found *B. welchii* and other anaerobic organisms in large numbers in pellagrous stools, and have suggested the provision of sanitary privies for preventing the spread and finally eradication of the disease. Goldberger and his colleagues are of opinion that such facts as complete absence of the disease among the nurses and attendants in the hospital seem to refute the theory that pellagra is at all infectious. It seems that dietary instead of a specific infection is probably the cause. Experimentally it was found that even ingestion of skin scales, nasopharyngeal secretions and epidermal secretions of the pellagra patients failed to produce the disease in a number of volunteers and they remained completely healthy during an observation period of six months.

Certain facts have recently been brought to light which show that in many countries where pellagra is very common, e.g., in Egypt, some

associated infections of the intestine may be found. Biggam and his associates (1933) in a large series of cases found that 94 per cent. of these patients were infected with helminths. Lane is of opinion that in addition to the deficient nutrition caused by dietetic deficiency, helminthic infection may also be responsible for such condition. Many workers have reported that schistosome infections predispose to an attack of pellagra and so also coexisting infection with amoebic or bacillary dysentery.

Treatment. The available evidence at present suggests that this disease is not contagious, isolation of the diseased individuals is therefore useless. A proper well-balanced dietary is the essential factor in preventing the occurrence of pellagra.

The disease shows periods of quiescence and exacerbations. Absolute rest and removal from the surroundings are of great benefit. Hydrotherapeutic measures have also been advocated; drinking of large quantities of water, cold abdominal compresses, hot packs and saline baths are said to alter favourably the course of the disease.

Diet. The dietary in treatment is the most important factor to be considered. In Italy where there was an epidemic of pellagra following the consumption of diseased maize, special measures were undertaken by providing grain-drying appliances for bakeries and other hygienic procedures together with dietetic treatment of individuals. This considerably reduced the incidence of the disease. Statistical records of treatment of pellagra with food containing sufficient amount of P.P. factor are very convincing. In this respect the addition of 2 to 4 oz. of skimmed milk or 1 to 2 oz. of wheat germ or $1\frac{1}{2}$ pints of canned tomatoes or 1 oz. of pure dry yeast, per person per day to the food supply, has been known to reduce greatly the incidence of pellagra.

Milk, though not rich in pellagra-preventing factor, is one of the most important article of diet in the cure and prevention of the disease; about 1 quart of milk daily should be given if other articles such as meat, vegetables and fruits are not taken in sufficient quantities. Vegetables and fruits are not rich in the P.P. factor. In the treatment of a case, meat, eggs, tomato and yeast together with milk are recommended; dried yeast in doses of 15 to 30 gm, daily in addition to the usual dietetic

measures gives a satisfactory result. Goldberger and Tanner recommend the following diet in pellagra which they found very beneficial. They give 200 gm. of lean meat daily together with brewer's yeast in the form of a dry powder in doses of 50 gm. daily during the active stage and about 15 gm. during the period of convalescence. Rice husk has also been recommended, daily doses of 50 c.cm. of the watery extract are given, or a preparation of rice husk known as 'oryzanin' may also be employed.

Drugs. Drugs have only a secondary importance in treatment. Arsenic in large doses has been regarded as a drug of value especially as a tonic. Fowler's solution in doses of 5 min. may be given three times daily. Similarly, other arsenical compounds, atoxyl, soamin and salvarsan have also been recommended.

From the fact that wheat germ when given orally is known to cure pellagra; intravenous administration of a 10 per cent. solution of wheat germ in normal saline has been tried. This is said to improve the condition of the patient. Administration of liver extract has also been recommended and this should be carried on along with the usual dietary treatment. Liver extract may be given by the oral route or by the intramuscular or intravenous channels. In patients with severe stomatitis and glossitis it may be difficult to feed them and in such cases liver extract is said to have a great effect in reducing the local lesions. Ventriculin has also been tried but without any conclusive results.

Massive doses of iron are reported to have given satisfactory results. Biggam and Ghalioungui (1933) treated twenty-six typical cases of pellagra with iron; for the nervous manifestations they prescribe Bland's pill in doses of 150 gr. twice daily for a period of 6 to 8 weeks together with a well-balanced diet.

Intravenous injection of sodium thiosulphate is said to give satisfactory results. Sabry (1931) recommends 10 c.cm. of a 10 per cent. solution to be given intravenously and the number of injections varies from twenty to sixty.

LATHYRISM

Lathyrism is a common disease in certain parts of India, especially the United Provinces, the Central Provinces and several districts of Behar. In 1868 Irving stated that nearly 7 per cent. of the population of certain districts of the former were afflicted with the disease and Acton in 1922 found that in Rewah there were 60,000 cases chiefly affecting men in the early prime of life.

In India it has been held for a long time that lathyrism is due to certain poisonous substances occurring in the pea *Lathyrus sativa* (*khesari dal*). Buchanan in 1904 stated that continued consumption of *khesari dal* for some months together contributed to the causation of the disease. *Lathyrus* is a vetch, and the peas of three species, *L. sativa*, *L. clymenum*, *L. cicera* are used habitually as an article of diet in India and Algeria by the people. When consumed in moderate amount they do not produce any symptoms, but in times of famine increased consumption has given rise to epidemics of severe poisoning especially among the poorer classes who subsist on them. Besides in India outbreaks have also occurred in Italy, France and elsewhere in Europe. Occasionally similar symptoms have been produced in cattle. In the laboratory, feeding experiments give varying results as different species of animals vary greatly in their susceptibility to the poison. Fowls, pigeons, and partridges eat the lathyrus pea freely and with apparent immunity; ducks are readily affected. Some animals fatten on this pulse while others are immune. Horses are particularly susceptible and have often died. The outstanding symptom in animals is muscular weakness; in acute poisoning with large doses the motor nerves are depressed but in feeding experiments with repeated doses such an effect may not be observed. In chronic poisoning the deep reflexes are increased and in monkeys and horses spasmodic attacks may occur irregularly in addition to the parietic symptoms. Death results from paralysis of the respiratory muscles.

In man the symptoms are usually precipitated by exposure to cold, wet and fatigue. Sometimes there may be prodromal symptoms, such as pain, numbness and cramps. As a rule the patient suddenly feels the legs and loins heavy, there is dragging of the legs, increased reflexes and more or less inability to walk. Later, there may be extreme spasticity and rigidity of the leg muscles; the case may progress to such a condition that he can only move his hands and feet in a sitting posture. Sensory disturbances and muscular wasting are not generally evident which point only to a partial degeneration in the cord. But in many cases symptoms such as loss of control of bladder and rectum, tingling, formication, lightning pains, diminution of tactile, heat and pain sensations and marked muscular wasting have also been recorded.

The exact nature of the lesion, occurring in man is not known. In experimental animals no lesion of the spinal cord or nerves have been found, but well-marked degenerative changes in the ganglion cells of the grey matter of the cord, in the vagal and accessory nuclei of the medulla, in the lateral columns and motor nerve roots of the spinal cord, and in the recurrent laryngeal nerves together with thickening of the walls of the arterioles and capillaries in the spinal cord have been described in horses.

Though the disease has been attributed for a long time to the consumption of the lathyrus pea in sufficient quantity over a sufficient period of time, the exact factor responsible for its production is not yet settled. Acton (1922) describing some cases in Rewah stated that *Lathyrus sativa* peas caused paralysis and death in ducks, but after the pulse had been steeped in water the animals lived and thrived on it. This is due to the fact that the poisonous principle is soluble in water, and can be removed by soaking the grain for 24 hours in three changes of water. It has been found however that some crops will apparently produce lathyrism while others will not and the experimental work by various workers has given discordant results as to the poisonous properties of lathyrus. Howard, Simonson and Anderson (1925) in an elaborate study of the subject concluded that *khesari dal* (*Lathyrus sativa*) did not contain any poisonous bases at all, and did not produce symptoms of paralysis in ducks that had been fed exclusively on this vetch, provided it had been freed from a closely allied vetch, *Vicia sativa* (*akri* or *akti*). When *Vicia sativa* was given to ducks and monkeys in the proportion of 10 to 50 per cent. in the food, it produced symptoms of nervous disease very similar to those of lathyrism, followed by death. They concluded that lathyrus is chemically free from any poisonous alkaloids and that these grains are harmless and even nourishing to these animals. Though some of the symptoms resemble those occurring in human lathyrism they are not prepared to state, in the absence of definite pathological proof, that *akti* is the cause of lathyrism in man.

Acton and Chopra (1927) reinvestigated the problem of the part played by *Lathyrus sativa* in the causation of lathyrism; they concluded that lathyrism is due to a contaminating weed *Vicia sativa* in *khesari dal* and not to any poison in the latter. The non-germinating seeds of *Lathyrus sativa* freed of *akti* contain no alkaloid or toxic substances and similarly the seeds that have germinated for 48 hours and previously freed from *akti* likewise produce no toxic symptom in experimental animals. The toxic principle divicine resides in the contaminating weed. This is probably closely related to barbituric acid which forms a toxic principle in many drugs such as, veronal, luminal, etc. Divicine can be split into barbituric acid by hydrolysis when the two NH_2 groups are replaced by an H and O group and it is probably due to this hydrolysis of barbituric acid that some toxic substance is formed which acts

on the central nervous system. It has been found that doses of 50 mgm. of this toxic base can produce paralysis of the hind legs of guinea-pigs. The reason why lathyrism is not prevalent throughout the year is the fact that in ordinary years *khesari dal* is free from this contamination and hence no lathyrism occurs, but during the period of famine the diet of poorer classes of people is wholly made up of an imported variety of lathyrus contaminated with *akki*, as it is the cheapest food available at the time. Moreover when a deficient diet, such as a whole diet of *khesari dal* is consumed, the general resistance of the body is lowered so that the poison can act more powerfully on the individuals.

Young (1927) made a contribution of a different nature. As a result of extensive investigations he found this *akki* contamination to be so rare that it could have but little, if any, effect in producing symptoms of lathyrism. In his cases lathyrism occurred when *Lathyrus sativa* predominated in the diet. In addition an analysis of the diet of those people showed that there was marked lack of fat soluble vitamin A, and he is inclined to believe that lathyrism may be to some extent, a deficiency disease. Stockman (1929) conducted a series of experiments on different species of animals and stated that lathyrus peas contain a poisonous principle and it is the cause of lathyrism, but as it is present in very small amount, its isolation in a pure state and in sufficient quantity has proved to be extraordinarily difficult. Many samples of lathyrus peas are non-poisonous or practically so unless consumed in large quantities. In human epidemics not all those who consume the peas are affected. This is due to the fact that there is great difference in the susceptibility of different species and of individuals of the same species of animals to these poisons, and hence results are variable.

Stott (1929) on the other hand, carried out investigation on horses by feeding them both with *Lathyrus sativa*, *Vicia sativa*, and keeping one as control. At the end of 4½ months all ponies were in the same excellent condition and had put on weight. It therefore appears that experimental proof of the factor responsible for the production of lathyrism is not corroborative, and further investigation into the problem is necessary.

Prophylaxis and treatment. The prevention of the disease depends on the improvement of the economic condition of these people and abolition of the system of bondage that exists in some states of India at present. Howard suggests that *khesari dal* should be planted in drills and the contaminating *Vicia sativa* removed by weeding. This should be done not only in places where lathyrism is rife but also in those areas from where the imported grain is sent to the famine stricken areas. But in view of the divergent views on the part played by *vicia* in the

spread of the disease, no successful measures can yet be devised. Nourishing diet is obviously of value. There is no specific treatment. The paralysed parts should be kept warm; massage and electricity are indicated.

INFANTILE BILIARY CIRRHOSIS

In the tropics the liver is particularly liable to be affected in a variety of conditions. Malaria, kala-azar, amoebic dysentery, are all known to cause derangement of the functions of the liver. The frequency with which hepatitis or even abscess of the liver follows an attack of amoebic dysentery, if left untreated, is too well known. Malaria and kala-azar are known to produce cirrhosis of the liver with ascites. Various parasitic infections of the liver, such as hydatid cyst, bilharzial cirrhosis, etc., are of common occurrence in the tropics. The treatment of these conditions naturally lies in removing the cause of the disease. Reference to these has been made in appropriate chapters.

Besides the various affections of the liver enumerated, a form of cirrhosis of the liver, affecting especially children under one year of age, has been noticed. In India it is common in Bengal, Madras and Bombay Presidencies. As a rule it runs a more or less protracted course of about eight to ten months; sometimes the disease may terminate in death in 2 or 3 weeks.

The clinical picture of a case may resemble greatly the features of acute yellow atrophy or the hypertrophic cirrhosis described by Hanot. The recognition of a case of infantile biliary cirrhosis does not, as a rule, offer much difficulty. The classical signs of hypertrophic cirrhosis of the liver, such as enlargement of the liver, ascites, dilatation of the abdominal veins, jaundice, clay-coloured stools are present in the majority of cases. Some cases however are known to begin with symptoms of catarrhal jaundice followed by signs of acute necrosis and acute insufficiency of the liver. Ultimately the patient develops deep jaundice, oedema of the eyelids and lower extremities with a considerable amount of ascites, enlargement of the liver and sometimes of the spleen. The known causes of catarrhal jaundice, such as, congenital syphilis, enteric fevers, Wells disease and many chemicals including organic arsenicals, phosphorus, cinchophen, etc., may be excluded as causative agents in this condition. It has been stated that the condition is due to infection with a virus. Though definite proof of this is lacking, it is possible that the acute necrosis that occurs in these cases is due to superadded

toxæmia as a result of previous damage of the liver cells by the virus. That similar conditions may be produced by other agents is well known. Opie (1910) observed that acute necrosis of the liver results from combined action of chloroform and *Bact. coli*. Hurst and Hurst (1928) produced similar changes with the combined action of manganese chloride and *Bact. coli*. Findlay showed that the extent of damage to liver cells was far greater when arsphenamine was used. Similarly, other observers have noticed secondary infections with *Streptococci*, *Bact. coli*, *Bact. faecalis*, etc., in a large number of cases of cirrhosis of the liver in infants. Moon (1932) showed the presence of streptococci in the histological specimens of the liver in these cases. It thus appears that many of these cases may have a super-added bacterial infection in an already damaged liver.

The cases which develop the typical character of hypertrophic cirrhosis usually do not offer much difficulty in diagnosis. They usually show enlargement of the liver, as well as of the spleen, with ascites, well dilated veins on the chest and abdomen, irregular temperature, anæmia and marked emaciation. This form of cirrhosis is said to be more common among the children of the well-to-do families and it tends to run in certain families. Poynton and Wyllie (1926) stated that cirrhosis in infants is frequently associated with infantilism. Many of these cases undoubtedly present pictures of infantilism with stunted growth, delayed dentition and inability to stand or speak.

Although the aetiology of the condition is unknown, there is good ground for belief that some sort of toxin is at work. The toxin is said to be conveyed to the smaller bile ducts by the hepatic artery, resulting in the production of biliary cirrhosis with degeneration of the cells in the first instance and subsequent increase of intercellular connective tissue. Malaria, kala-azar, alcohol, etc., which are known to cause hypertrophic cirrhosis of the liver, probably do not play any part here.

Treatment. Treatment of this condition is far from being satisfactory. Whenever the disease is seen to run in families, the child should be removed from the endemic locality and artificially fed. Diet is of particular importance. A fat-free diet is generally advised, but not sufficiently defatted to impoverish the nutrition of the child; fruit juice and sugar should be added along with it. These cases show marked disturbance of the carbohydrate metabolism. The liver is poor in its glycogen store as it has been shown that on fasting, the blood sugar level is very low. Glucose along with insulin temporarily improves the condition of the patient; for this, 5 units of insulin should be injected coupled with 4 dr. of glucose by the mouth and repeated as the condition requires.

Constipation and tympanitis if developed should be treated on usual lines.

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CHAPTER II

METABOLIC DISORDERS

DIABETES MELLITUS

Diabetes is a disease which should prove to be of great interest to any one working in India not only because it is extremely common here, more particularly in Bengal, but also because the disease was known to the ancient Hindu writers as early as the 6th century B.C. Charaka (2nd century A.D.), the most renowned Hindu physician of his time, described some of the cardinal symptoms of diabetes (including the presence of sugar in the urine) in his *Charaka Samhita*. It appears that Charaka collected his materials from a much earlier work of *Agnivesa* who again based his writings upon the teachings of his master *Atreya* (6th century B.C.). It is a disease which may be said to have its home in the tropics. What gout is to the nobility of England, diabetes is to the aristocracy of this country. Among the ancient Greek writers, the symptomatology and prognosis of diabetes are to be found in the writings of Celsus (25 A.D.). The name diabetes (which means 'to pour through a syphon') was given by Arateus in 30 A.D. Among the European writers Thomas Willis, an English physician of repute, first noticed the characteristic sweet taste of diabetic urines in 1670, thus establishing the basic principle for diagnosis between diabetes mellitus and diabetes insipidus.

Ætiology. The consensus of the present day opinion is that a pancreatic lesion plays the most important part in the ætiology of diabetes and that the root cause of diabetes centres round the islands of Langerhans, though the nature of the factor or factors giving rise to the diseased condition of the islet cells has not yet been clearly understood. The predisposing causes which directly or indirectly are likely to throw undue strain on the islet cells of the pancreas and cause their hyaline degeneration and atrophy sooner or later are many, the more important among them being sedentary habits, lack of physical exercise, ill-balanced diet, overeating, too much mental work, infections, etc.

Heredity is also believed to be an important factor. In some of the writer's series of cases, diabetes could be traced to run for three or more generations.

Climate is also believed by many to be one of the factors. It has been stated that tropical and sub-tropical climates lower the carbohydrate tolerance of individuals. Basset-Smith has observed that under the influence of the tropical heat, there is a tendency to the retention of carbonic acid in the alveolar air in people at rest and also to the production of glycosuria and acidosis particularly in the well fed.

Coming to the incidence of diabetes among the different races of India the writer is of opinion that Bengalee Hindus appear to be more prone to diabetes than any of the other races, the proportion being 54 per cent. among the total cases.

Infections of any kind may prove to be a direct cause of diabetes, probably owing to some kind of damaging effect on the pancreas by the toxin. Lawrence and Buckley have proved by experiments that diphtheria toxin will practically annul the action of insulin.

Symptoms. Clinically two principal forms of diabetes are recognised, acute and chronic. The acute form is generally found among young people and usually runs a rapid course. Mild chronic forms of the disease are usually common in middle aged persons but such cases may gradually develop into the severer form and then the disease runs the usual rapid course.

Most cases of diabetes complain of unwonted lassitude, loss of strength, loss of weight, polyuria and thirst as symptoms at the onset of the disease. Constipation is almost always a constant feature. Loss of sexual desire or even sexual impotence is also a common symptom and frequently an initial one.

Diagnosis. The diagnosis of true diabetes mellitus is often an easy matter when the patient presents the usual signs and symptoms, but there are many cases in which considerable difficulty is experienced and elaborate laboratory methods of diagnosis are necessary.

The average normal fasting level of blood sugar in man is 0.1 per cent. After a meal consisting of carbohydrates, the blood sugar rises reaching a maximum level of 0.17 per cent. within one hour and coming down to the normal level again, usually within 1½ to 2 hours. The reason why it comes back to the normal level is because a part of the extra sugar is changed into glycogen and stored as such in the liver and part of it undergoes combustion in the muscles and tissues. In the diseased condition, the picture is quite different for owing to the inability of the diabetic individual to store sugar as glycogen or burn it like a normal person, the circulating blood of the diabetics contains excess of glucose. Thus in mild cases, the fasting level is usually found to be 0.13 per cent. or over. In more severe cases, it is of course proportionately higher, according to varying degrees of defect in the storage mechanism. Thus for practical purposes, it is

usually assumed that a 'fasting level' of 0.13 per cent. or over indicates a condition of diabetes mellitus.

In many cases of potential diabetes and even in cases of mild diabetes, however, the fasting level of blood sugar may be perfectly normal and the urine may be aglycosuric even after meals owing to a varying *leak point*. In such doubtful cases, the *glucose tolerance test* should be done and the behaviour of the blood sugar after a glucose meal should be investigated. A healthy normal person should conform to the following:—

- (1) The fasting blood-sugar level should be normal.
- (2) The maximum rise of blood sugar after ingestion of 50 gm. of glucose should take place within one hour and should not go beyond 0.17 per cent.
- (3) The drop of the blood sugar to the normal level should take place within 1½ hours after the glucose is taken.
- (4) No glycosuria should occur.

A diabetic blood-sugar curve after a glucose meal deviates from the above according to the varying degree of defect in the storage mechanism, judged according to the rise of the initial (fasting) level of blood sugar, a tendency to a much heightened curve and a much delayed return to the normal level.

Treatment. The fundamental principle underlying the successful treatment of diabetes is based on the knowledge that a careful adjustment of the diet, with or without the use of insulin as an adjunct, will prevent hyperglycæmia and hence eliminate glycosuria and thus will tend to give rest to the already overworked and diseased islet cells of the pancreas. There is plenty of evidence in the literature to prove that if hyperglycæmia can thus be prevented, the progress of the disease will be arrested gradually, the distressing symptoms of the disease will disappear and in the majority of cases the 'tolerance' of the patient will improve considerably.

Thus it appears that the treatment of diabetes mellitus falls mainly into two main groups:—

(1) *Dietetic treatment.* This means that the patient should be given only that amount of food which is absolutely necessary to meet the minimum metabolic requirements of the body. This is known as the *basal diet*.

(2) *Insulin treatment.* It should be remembered that insulin treatment is only a valuable adjunct to the dietetic treatment for which it can, in no sense, be considered to be a

substitute. The indication for insulin treatment will be considered later on.

I. Dietetic treatment. In calculating a basal diet for diabetic patients the following points should be considered:—

(1) The caloric value of the diet should not be less than 25 calories per kilo. of the patients' body weight.

(2) The protein content of the diet should not be less than the proportion of about 0.75 gm. per kilo. of the body weight.

(3) The ratio of fats to carbohydrates in a diabetic diet should not be more than 2.5 to 1. This proportion is necessary to balance the ketogenic component of the diet with the anti-ketogenic component and is aimed at preventing acidosis.

Bose's formula for calculating the basal diabetic diet is given below:—

Total caloric requirement of the patient	=	Weight of the patient in kilo. \times 25
Protein requirement in grammes	=	$\frac{\text{Total caloric requirement}}{88}$
Carbohydrate requirement in grammes	=	$\frac{\text{Total caloric requirement}}{80}$
Fat requirement in grammes	=	$\frac{\text{Total caloric requirement}}{12}$

Thus a diabetic individual weighing 72 kilo. will require the following diet.

Total caloric requirement	=	72×25	=	1800 calories.
Protein requirement	=	$\frac{1800}{88}$	=	54.0 grammes.
Carbohydrate requirement	=	$\frac{1800}{80}$	=	60.0 „
Fat requirement	=	$\frac{1800}{12}$	=	150.0 „

It will be seen from the above that the protein ratio of the patient is in the proportion of 0.75 gm. per kilo. of the body weight. The proportion of fat to carbohydrate in the diet is also in the proportion of 2.5 to 1.

The number of gramme of carbohydrate, protein and fat and the caloric value of the diet required being thus ascertained, the patient's diet is framed by the use of food tables.

For ready reference, a sample diet chart (suitable for a diabetic patient weighing 72 kilo. as mentioned above), having the above proportions of food principles is appended below :—

Bran bread (or wholemeal atta)	3 oz.
Butter	2 oz.
Eggs	2 only
Fish or chicken	4 oz.
Mutton	4 oz.
Green vegetables	12 oz.
Milk	8 oz.
Cream	1 oz.
Ghee	2 oz.

Approximately, Carbohydrate = 60 gm. ; Protein = 54 gm. ; Fat = 150 gm. ; Calories = 1800.

On a diet calculated as above, the average diabetic patient of the mild type usually becomes sugar-free in about four days and the blood sugar comes down to the normal level in about a week's time. If however the patient does not become sugar-free or does not maintain the blood sugar at the normal level on the above diet, insulin treatment is usually indicated.

II. Insulin treatment. As mentioned before, insulin treatment in cases of diabetes should be considered as a valuable adjunct to the dietetic treatment in order to get the full benefit of the insulin and the quantity of diet allowed. It should also be kept in mind that unlike most drugs, insulin has no fixed dosage and that no hard and fast rule can be laid down regarding the dosage of insulin, inasmuch as it may vary in individual cases, according to the severity of the case, the complications, the diet prescribed and various other factors.

Another important factor which should be considered is that the amount of glucose utilised per unit of insulin varies in different cases. It has however been roughly estimated that one unit of insulin usually causes 1 to 2 gm. of carbohydrates to be utilised in a moderately severe case of diabetes. In a milder case, the carbohydrate utilisation per unit of insulin is somewhat greater. This fact should be borne in mind in selecting the proper dose for a given patient.

Roughly speaking, the total amount of available glucose calculated from the patient's diet minus the total amount of glucose passed in the urine will indicate the carbohydrate tolerance of the patient and the amount of glucose which is over the limit of tolerance, *i.e.*, the total amount excreted in the urine) must be covered by an adequate dose of insulin calculated in the way mentioned above.

A few general hints on insulin treatment

1. There are no hard and fast rules regarding the dosage of insulin in a particular case as it varies with the complications and the amount of fasting hyperglycæmia. It is always best to begin with a small preliminary dose (about 10 units).

2. Insulin is certainly indicated in all cases of severe diabetes mellitus with pronounced hyperglycæmia and marked glycosuria with or without ketosis.

3. Insulin is also indicated in the milder forms of the disease where a careful dietetic regime has failed to remove glycosuria or reduce the fasting hyperglycæmia, say below 0.15 per cent.

4. It is always best to give insulin injection, 20 minutes to half an hour before meals.

All forms of hard or strenuous exercises should be forbidden for at least 3 to 4 hours after insulin injection.

6. Roughly speaking it may be assumed that one unit of insulin causes 1 to 2 gm. of carbohydrates to be utilised in a moderately severe case of diabetes. In milder cases the carbohydrate utilisation per unit of insulin is greater.

Insulin Hypoglycæmia, its Symptoms and Treatment

Early symptoms. (1) Unaccountable nervousness. The patient feels some impending danger. (2) Listlessness. (3) Tremulousness or actual tremors, particularly of the extremities. (4) Dim vision sometimes diplopia. (5) Great desire for food—a sinking feeling in the pit of the stomach. (6) Vasomotor disturbances—pallor of the face alternating with flushing and sweating. (7) Palpitation of the heart.

Late symptoms. (8) Mental confusion—low muttering delirium. (9) Loss of deep reflexes. (10) Muscular twitchings and convulsions. (11) Coma.

Treatment. The treatment is simple if undertaken early. The patient should be put to bed. A tablespoonful of glucose powder dissolved in water and given by the mouth is the best but if it is not at hand, ordinary table sugar will form quite a good substitute. Orange juice 4 to 8 oz. may also be given, if available. If the symptoms persist after $\frac{1}{2}$ hour more sugar should be taken. If the milder symptoms are overlooked or not given heed to and they are allowed to pass on to the coma stage, $\frac{1}{2}$ to 1 c.cm. of solution adrenaline chloride (1 in 1,000) should be given intramuscularly. Glucose may be given intravenously, if necessary.

Hypoglycæmic and diabetic coma. A diabetic patient may become comatose because he has either too little or too much insulin. Two kinds of coma are generally recognised and the signs and symptoms following one should be distinguished from the other.

In insulin (or hypoglycæmic) coma the normal colour of the skin is generally preserved or it may be very white. The respirations are shallow but the breath does not smell of acetone. The urine is usually sugar-free and does not contain aceto-acetic acid but may contain both if the bladder has not been emptied for some hours. The blood sugar is below 0.07 per cent. or may be as low as 0.04 per cent. In diabetic (or hyperglycæmic) coma on the other hand, the symptoms are fortunately quite characteristic. The skin is usually flushed, the respirations are deep and the breath smells of acetone. The urine always contains large amounts of sugar as well as aceto-acetic acid and the blood sugar is over 0.2 per cent. and may be even as high as 0.5 to 0.8 per cent. In hyperglycæmic condition, if the patient is not deeply comatosed the initial dose should be 50 units but if coma be deep 70 or over 100 units of insulin should be injected at a time. But if the patient is used to large doses of insulin, the initial dose should be at least half as great as the doses recommended for ordinary cases. Administration of sugar is always desirable along with the

injection of insulin to avoid hypoglycæmic coma. In cases of deep coma, 600 c.cm. of a 2 per cent. solution of sodium bicarbonate should be given with 50 gm. of glucose. Along with the insulin and glucose treatment estimation of blood sugar where possible and particularly the testing of urine for sugar every three hours should always be done to note improvement of the patient. A repetition of treatment may be necessary where improvement is slight or even absent. The second course of treatment usually begins six hours after the first one. If the patient is better, half the initial dose of insulin should be given; if no improvement follows the initial treatment, the previous dose should be repeated; and if the patient is worse, the dose should be half as much again.

The risk of precipitating a hypoglycæmic coma should always be borne in mind while carrying on insulin treatment for diabetic coma. The most usual sign in such cases is a relapse into deep coma after a partial recovery of consciousness. This emergent condition demands prompt treatment. One c.cm. (ten units) of pituitrin or one c.cm. of adrenalin should at once be injected and this is to be followed by an intravenous injection of 300 c.cm. of 20 per cent. glucose solution. The treatment raises the blood sugar and the patient regains consciousness. In the following lines a general outline of treatment is given.

1. Put the patient in bed in charge of a trained nurse. Keep him warm with blankets and hot water bottles, if necessary. If there are indications of circulatory collapse, give digitalin, caffeine, camphor or other suitable drugs.

2. Evacuate the large bowel by an enema. If there is much vomiting gastric lavage should be done.

3. Give insulin as soon as possible. No hard and fast rule can however be laid down regarding the initial and the subsequent dosage of insulin and the mode of its administration in as much as it depends on the depth of the coma, the general conditions of the patient, the blood-sugar level and various other factors. As a general rule, it may be said that in a case of moderate severity, an initial dose of 40 to 50 units or more of insulin may be given subcutaneously or intraven-

ously, followed by the same amount of glucose in grammes, administered by mouth if the patient can swallow, or intravenously if the patient is totally unconscious.

4. In severe cases, where there is severe dehydration due to loss of fluid and collapse, prompt treatment is essential to save the patient from death, and the case is to be treated on similar lines as in cholera. Introduction of saline intravenously, subcutaneously and rectally should be done as early as possible. It is best to combine 10 per cent. glucose with normal saline. One pint of this solution will contain 60 gm. of glucose and should be given very slowly by the intravenous route immediately after the insulin injection. The injection of 0.5 c.cm. of adrenalin chloride solution (1 in 1,000) in addition sometimes helps in restoring the feeble pulse. This may be repeated after 4 hours according to the state of the collapse. If the patient's condition improves sufficiently, only insulin and glucose should be continued. The dose of insulin will however have to be varied according to the state of the acidosis and hyperglycaemia, judged from the urine and blood-sugar test. The dose of glucose should also vary according to the amount of insulin given. Rectal saline should also be given. Solution of the same strength as used for intravenous injection may be given. Sodium bicarbonate (1 dr. to a pint) may be added to the fluid with advantage ; 4 to 6 oz. of this fluid should be introduced per rectum very slowly every 4 hours.

OBESITY

Obesity is excessive accumulation of fat in the body. For practical purposes it may be defined as a condition in which there is an increase of about 20 per cent. of fat over that found in an individual of average weight. The weight of the person therefore is 20 per cent. over the normal for his age and height. The condition of obesity is frequently met with in tropical climates, and particularly among certain classes in India who indulge in foods rich in carbohydrates and fats and take little exercise. The condition runs in families and

there appears to be an hereditary tendency towards its production.

The effects of such a condition on the physical and mental processes of an individual are obvious. Fat-laden persons are known to be more liable to microbic infections. An extraordinary degree of impairment of muscular efficiency and signs indicative of cardiac embarrassment can be found in these people. Fatty changes in the heart muscle and abnormal blood pressure are frequent accompaniments. As a general rule, obese persons avoid effort, both mental and physical, and their critical faculties are to a considerable extent dulled. In addition certain other common maladies such as constipation, dyspepsia, osteo-arthritis, etc., are frequently observed in these cases. The effect of obesity in causing sterility in women has been recognised. It has an additional importance from the æsthetic point of view.

It is customary to describe two varieties of obesity :—(1) *Exogenous obesity*, in which there is a faulty balance between the intake of food and the output of energy, and (2) *Endogenous obesity* which is due to obscure constitutional factors, such as endocrine or metabolic disturbances. In practice, however, it is found that a clean cut distinction cannot be made between the two varieties and many cases of obesity present the features common to both conditions.

Exogenous obesity. It is almost an axiom that obesity is due to over-eating. In these cases there is a great disparity between the intake of food and the output of energy in the shape of muscular work. Poulton (1931) observed that most people keep the same weight from year to year which means that the amount of food taken is exactly balanced by the amount burnt in the body. Three processes are responsible for this, namely (i) the so-called basal metabolism of the individual, (ii) specific dynamic action of the foodstuffs, which means that when food is taken its metabolism in the body leads to increased burning, and (iii) exercise which increases combustion to supply the extra energy required. Hence to maintain the normal weight there must be a close relationship between the food taken and the activities of the individual. If the quantity of fuel taken as food is much in excess of what the organism requires there will arise a tendency to obesity, and when this is continued for a long time it may result in deposition of considerable fat. Obesity in the adult is in a very large proportion of cases due to over-eating. During childhood and adolescence, the amount of exercise one takes precludes any deposition of fat. As youth merges into middle age, violent exercise is replaced imperceptibly by exertion of a less drastic

nature. Hence it naturally follows that when utilization of foodstuffs is no longer so large, the amount of food during the period should be curtailed. If that is not done, an accumulation of fat occurs in many cases.

Certain foodstuffs are particularly liable to cause accumulation of fat in the body. In addition to the use of fat-forming foods, malt liquors are also known for their fattening properties. Intemperance in the use of alcohol is also an important factor, for alcohol is readily oxidized and thus allows the fat already formed to remain undisturbed. A suggestion was put forward by Weber (1928) that exogenous obesity may be the result of pancreatic stimulation following the ingestion of too much carbohydrates.

Endogenous obesity. Constitutional obesity. While it is possible to attribute corpulence in some persons to dietetic excesses it is well known that certain obese people eat remarkably little and yet have a tendency to accumulate fat. Strouse and others (1924) observed that obesity might occur in certain persons on intakes much below the necessary caloric requirements, the cause of which is imperfectly understood. It is, therefore, believed that this type of obesity is brought about by a qualitative anomaly in metabolism, *i.e.*, an abnormally increased transformation of carbohydrates into fat, and thus even with caloric intake which is much below the normal, such a patient will convert fat from the carbohydrates and store it as such. The part played by heredity in causing so called constitutional obesity is not definitely understood. It is said that the maternal factor is more important in this connection, but how far it is due to constitutional cause or over-eating, remains to be settled.

The endogenous type of obesity is said to be more common in women than the exogenous variety. This is in conformity with the fact that sudden increase in weight is commonly observed in women at puberty, after child birth and at the menopause. In man this change during the middle years is less sudden. Nevertheless changes in the testes, hypertrophy of the prostate and analogous changes in other endocrine glands may occur; this is probably due to a general lowering of the activity of the catabolic glands. As a result of this many people show a tendency towards accumulating fat.

Endocrine obesity. The part played by endocrine glands in the causation of obesity is important and interesting. Obesity associated with thyroid deficiency with the clinical picture of myxedema is well known. In these cases the classical features are coarse facies, thick lips, puffy eyelids, dry skin, etc. Thyroid deficiency is unquestionably responsible for a large number of cases. The pituitary gland also plays an important part in the causation of obesity. Hypopituitarism (Frolich's syndrome) is a commonly recognised condition. It has also been shown that so-called pituitary obesity can be experimentally produced by injury to the hypothalamic region. Langdon Brown (1931)

stated that the pituitary plays an important rôle in the production of some forms of obesity, but the relationship of the pituitary gland to obesity is complicated by the fact that lesions of the hypothalamic region produce identical changes.

Gonadal insufficiency is also responsible for a certain number of cases. Furthermore there exists a close relationship between the thyroid, pituitary and the gonads. Lambie (1931) described various syndromes resulting from the interaction of gonadotropic, thyrotropic and growth-promoting factors of the anterior portion of the pituitary gland. The commonest example of these cases is a combination of pituitary and thyroid obesity. Such conditions as Dercum's disease (*adiposis dolorosa*) and the Lawrence-Biedl syndrome have been described.

In women, among the endocrine glands, thyroid and ovaries have been chiefly incriminated as the cause of obesity. There is no doubt that these glands play a great part in the life of a woman. Many cases of obesity in women are known to show a rapid loss of weight after thyroid treatment. The part played by the ovary is not definitely understood. In menopausal obesity ovarian hormone has given variable results.

The influence of insulin as a cause of obesity was originally suggested by Fala. Poulton (1931) discussed this theory of excessive production of insulin as a cause of obesity. It is suggested that diabetic patients treated with insulin develop obesity and that insulin along with carbohydrates helps to fatten lean people. The sugar tolerance is increased in some cases of obesity which is compatible with an increased output of insulin. This theory has not been universally supported.

Treatment. Whether alimentary or endocrine in origin, the treatment of obesity is entirely a matter of dieting with the exception of some cases of hypothyroidism.

Diet. The underlying principle is to give a diet of caloric value below that required for the optimum weight of the patient. As a general rule it should be 20 to 25 per cent. below his normal requirement. Great care should at the same time be taken in preserving the proper nitrogen equilibrium of the patient which is of great importance. The diet should be arranged in such a way that the patient is forced to burn his own fat without the loss of his body proteins. This is not difficult to accomplish provided the diet contains sufficient proteins and is of a low caloric value. Usually, 1.5 gm. of proteins per kilo. of the body weight will answer the purpose. It should also be remembered that carbohydrates in the food, besides being the chief source of energy for the

maintenance of the body temperature and for the production of work, are most efficient protein spacers and every use should be made of them to preserve the nitrogen balance at an economic level. At least 50 per cent. of the energy contained in the food should come from the carbohydrates. Thus, in calculating a reduction diet, the caloric value of the protein allowance should be calculated first and to this should be added an amount of carbohydrate sufficient to bring the caloric value up to the desired total caloric intake. Fats need not form an item of any importance in the dietary of obese persons.

According to Browning (1934) the essential factors in the choice of a dietary are —

(1) **Preservation of nitrogen balance.** To do this the proportion of protein to carbohydrate should be about 1 gm. of protein to 0.6 gm. of carbohydrate with a total of not less than 60 gm. of protein.

(2) **Minimum fat intake.** As already stated fat is cut down from the dietary so that the patient is forced to burn his body fat to supply the metabolic need.

(3) **Avoidance of hunger.** This can be avoided by giving high proportion of fruits and vegetables which have low caloric value.

(4) **Maintenance of water balance.** Sometimes the patient shows a tendency to store water in the tissue though he may be losing a good deal of fat. This is prevented by giving a salt-free diet and increased quantity of protein.

(5) **Adequate mineral and vitamin content.** The loss of mineral content with the use of the recommended diets is not great. If the fat is very much restricted, there is likelihood of the vitamins A and D being reduced below the standard level. This can be remedied by giving carotene and irradiated ergosterol. A cup of yeast extract once a day will supply vitamin B.

(6) **Physiological factor.** It is in many cases difficult to induce a patient to change to a diet of small quantity and simple character. Under these circumstances a slow reduction is preferable to a drastic one, the foods should be distributed over the various meals allowed, to make them as palatable as possible.

A very efficacious diet (modified by Douthwaite, 1934, from Williams) is given as follows:

On waking. A glass of water. *Breakfast.* Tea or coffee, sweetened with saccharine; one slice of dry toast, no butter; 3 oz. of cold tongue, boiled sole, haddock, or whiting; fresh fruit. 1 p.m. A tumbler of

water. *Lunch.* 4 oz. of chicken or meat (except pork), but no gravy; vegetables as given below, cooked without fat; salad without oil; one square of vita-weat; fresh fruit. 5 p.m. Tea without milk or sugar.

Dinner. Bouillon; fish; 2 to 3 oz. of game or meat (except pork), no bread-sauce or bread crumbs; vegetables as mentioned below; salads; one slice of toast; dry wine; fresh fruits; coffee with saccharine. *Condiments are allowed.* Worcester and anchovy sauces, ketchup, pepper, mustard, vinegar, walnut pickle, horse radish, salt sparingly.

Vegetables allowed. Green vegetables (except peas), celery, seakale, asparagus, and salsify.

Another form of dietary has been devised by Evans and Strang (1929); one gramme of protein per kilo. body weight is given along with some carbohydrate to maintain nitrogen equilibrium.

Evans and Strang Diet (about 650 calories)

Breakfast. One egg and 1 oz. of bread. *Lunch.* One egg and 4 oz. of vegetables as below. *Dinner.* One cup of bouillon and 3 oz. of lean meat; 4 oz. of vegetables. *Vegetables allowed:* Lettuce, cucumber, spinach, asparagus, endive, celery, mushrooms, tomatoes, sprouts, watercress, cauliflower, radish, cabbage.

Water as much as needed; no fried foods; a teaspoonful of bicarbonate of soda daily.

It is essential to eat the whole amount mentioned in this diet. A modification of this diet is given by Dodds (1934) which allows only 8 calories per kilo. Though efficacious it is rather drastic. There is a tendency to acidosis with Evans and Strang diet, which may be relieved by the use of sodium bicarbonate.

Kenyon's modification (1933) is to give 1,000 calories which allows high protein, vitamin and mineral salt.

Breakfast. One portion of fruit; one egg and white of one egg; coffee, tea, bread substitute (for example, Heudebert's breadsticks). *Lunch,* 3 oz. lean meat, fish, or fowl; $\frac{1}{4}$ pint 5 per cent. vegetables; one portion fruit. Tea. *Dinner.* 3 oz. meat, fish, or fowl and vegetables as at lunch. 9-30 p.m. Half-cup orange juice; 1 oz. lemax. In addition, 1 $\frac{1}{4}$ glasses skimmed milk daily (for calcium content); one capsule haliverol t. i. d. (for vitamin content).

A fruit portion—one orange; half a grape-fruit; one medium apple; two medium peaches; one small pear; one cup strawberries; one cup blackberries.

It is important to control the body weight by weekly measurements. When the desired weight has been obtained, the diet is slowly increased.

Exercise. The therapeutic factor next in importance to the restriction of food is the stimulation of the metabolism by physical exercise. Exercise hastens the metabolic rate and leads to increased oxidation of the ingested food, or, if sufficient food is not available, of the body fat. The exercise should be gradual and regular and should not be carried up to the point of exhaustion.

Cold bath. The other factor which also serves as a useful physical stimulus to metabolism is a cold shower or plunge bath and should be advocated where there are no contra-indications for it, such as, severe myocardial degeneration, arteriosclerosis and high blood pressure.

Endocrine therapy. As it is possible to control obesity with dietetic restrictions in many cases, endocrine therapy should not be indiscriminately resorted to. Thyroid has been too frequently used to stimulate metabolism and reduce weight. In those cases where the basal metabolic rate is below normal, the patient will probably lose weight after thyroid medication. Unless properly controlled, even in cases of myxoedema, the weight after an initial fall may be increased after administration of thyroid. In thyrogenous obesity and other forms where metabolic stimulation is required, thyroid should be used in doses of half a grain twice daily; this is gradually increased to 1 gr. three times a day. Some cases may require much larger doses. Other endocrine preparations such as pituitary, or combination of thyroid and pituitary, or treatment by extracts of genital glands have been advocated, but the effect of such therapy after oral administration seems to be uncertain.

Drugs. It has been shown that certain nitrophenols are capable of causing a marked increase in both the temperature and oxygen consumption. Cutting and his co-workers (1933) found that by using a drug of this nature, which is 2:4 dinitrophenol, the metabolic rate of animals could be raised by 50 per cent. by a dose of 10 mgm. per kilo. body weight. In

human beings the drug in doses of 3 to 5 mgm. per kilo. body weight daily raised the metabolic rate by 40 per cent. and this was accompanied by an average loss of weight of 2 lb. a week. As this compound has been known to be toxic, Dodds and Pope (1933) working with dinitro-o-cresol (dekrysil) found that it would produce the same effect in much smaller doses—1 mgm. per kilo. daily. Douthwaite (1934) has used this drug in doses of 1 mgm. per kilo. thrice daily, and later once daily; though the constitutional effects were not marked with smaller doses, the loss of weight was very insignificant. These drugs are in the experimental stage and should, therefore, be used with caution.

In addition to these measures, other methods of therapy have a great bearing on the final success in treatment. Excretion of waste products of metabolism should always be favoured, and with this end in view the activities of bowels, kidneys, skin and lungs should be watched

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CHAPTER III

TROPICAL NEURASTHENIA

The term neurasthenia has been defined in various ways by different neurologists and psychiatrists. Collier considers the condition to be a pathological weakness without discoverable lesion, manifested by rapid and great fatigue, physical or mental, or sometimes both. It is characterised by functional exhaustion of the tissues especially those of the nervous system due to excessive or undue waste of nervous energy. psychic or motor, and in some cases to acute intoxication. The condition, no doubt, is essentially one of emotional unbalance with loss of mental stability, associated with undue irritability to external impulses. Neurasthenics always experience a sense of fatigue or muscular weakness and complain of being unable to do mental labour, the least concentration being followed by vertigo, headache, etc.

According to Dercum this readiness of fatigue is the primary and fundamental symptom of neurasthenia. Beard in his treatise on "The Nature and Diagnosis of Neurasthenia" brings out the literal meaning of the term as a state of nervous exhaustion and he divides the condition into definite separate clinical groups as cerebral, spinal, gastric, cardiac and sexual. His views though open to discussions ultimately succeeded in gaining a general acceptance from a large number of modern psychiatrists. It is generally held that such a condition of neurasthenia does never exist, but nevertheless a great variety of conditions in the tropics where any specific cause cannot be discovered is termed as an idiopathic disease 'neurasthenia.' The modern idea however is that there is some underlying factor causing the train of symptoms constituting neurasthenia. Investigation into the subject reveals that neurasthenia is associated with certain existing causes. Tropical neurasthenia responds to treatment more readily than the ordinary kind, change of climate being especially beneficial.

As neurasthenia is considered to be a condition of nervous exhaustion one should have some knowledge of the working of the nervous system and of nervous energy in particular. The working of the mind and the display of energy arising from the normal physiological processes within the body are all due to an outflow and sometimes of an overflow of the energy inherent in and manufactured by the highly

complex protoplasm (neurokyme) of the neurones of the higher nervous system, and this is attended by structural changes, e.g., chromatolysis in the cells. Neurasthenia was for a long time attributed solely to exhaustion of the nerve centres presiding over general nutrition and particularly of the brain and nervous system. Actual loss of substance in the cells and especially in the nucleus has been noted by many workers. Impaired metabolism with accumulation of waste products in the system gives rise to auto-intoxication affecting especially the nervous system and the functions over which this system presides are correspondingly impaired. In this condition if the patient persists in imposing upon his weakened organism even slight tasks, a vicious circle of pathogenic activity is formed which encourages a further waste of energy.

Left to itself neurasthenia tends to persist, unless its cause is removed. Under proper prophylactic measures and judicious treatment the prognosis is favourable, especially in the cases where organic changes have not had time to undermine the functions of the organs secondarily involved.

Ætiology and incidence in the tropics. From a study of the causes of neurasthenia, the condition has been well classified as :

I. Primary or independent of any discoverable exciting causes, this has been termed 'congenital' or prenatal. Heredity acts only as a predisposing influence through parental neurosis or psychoses. No gross visceral damage, nor any evidence of serious illness or infection is met with in this type. The signs and symptoms are chronic in nature or a recurrent one. A careful history will reveal that the individual belongs to a stock of similar victims and this is essentially one of a familial nature. This type of neurasthenia is very common in the tropics and mostly met with among children in the same family. They manifest it more and more with age, at a period of life during which great exertion and anxiety combine to increase the wear and tear of the central nervous system and indirectly of the organism at large. Climatic influence in the tropics and the faulty upbringing of children in such families account for the development of such a state of mind and brain in them. They can carry on the ordinary routine of life but any slight deviation from it will surely throw them out of gear resulting in signs and symptoms of nervous exhaustion. The picture may be well drawn of such a neurasthenic as suffering from various bodily pains (paræsthesias), abnormal sensations of the brain, heart and stomach (hypochondria). The appetite is capricious, ravenous one day and bad the next day. In short, the whole condition is one of 'irritable weakness with hypochondrial trend.'

The underlying psychopathology of these primary neurasthenics is that the cell units and the neurokyme in them are not sufficiently strong to keep in check and in store the potential energy responsible for the normal body functions. A continuous drainage of such energy

demanding by an increased body activity, with which the inherently defective neurones cannot successfully keep pace, throws the whole system out of balance resulting in a condition of neurasthenia.

II. The second group constitutes a larger number of ætiological factors and they all come under the type of secondary neurasthenia, secondary to some primary causes such as physical ill-health with lowered vitality, condition of life incompatible with environment, overwork, emotional stress. It is rightly said that it is not the work but the worry that kills. Sudden physical and mental shock, continued conditions of fear as seen in maniacs when they are not actually suffering from any disease, sometimes predispose to an attack of neurasthenia.

Besides the factors mentioned there are others met with. People in the tropics live in a climate in which humidity is added to heat and this will act as a primary causative factor. There are diseases also which are peculiar to the tropics and are seldom seen elsewhere. All these affect the daily lives of the people in a way different to the people of temperate zones. The maladies and the physical agents such as extreme changes of weather, occurring in tropical countries are responsible for the chronic ill-health of people and should be considered as factors bringing about a series of signs and symptoms constituting the so-called condition of neurasthenia. Such causes may be conveniently classified as (a) exciting, (b) predisposing, and (c) general endocrine dysfunction.

(a) **Exciting causes.** The debilitating after-effects of acute fevers in the tropics, exposure, indiscretions in diet, insufficient or improperly selected food, etc., are potent factors of after-neurasthenic symptoms. All convalescents after acute maladies either promptly recover without after-effects or may suffer from chronic ill health for a long time with symptoms of neurasthenia. Various forms of enteric fevers, dysentery, cholera, intestinal helminthiasis, etc., give rise to disturbances of the gastro-intestinal functions. The continuous absorption of toxins elaborated lowers the resistance of the organism as a living entity (not only of the nervous system), undermines the metabolic dynamism and prepares the soil for neurasthenia.

Individuals so predisposed represent by far the majority of cases. Women suffer almost invariably with uterine diseases in connection with neurasthenia. Excessive fecundity, dysmenorrhœa and menopause are thought to exercise a marked exciting influence. Disorders of the female organs which affect the nutrition of the nervous system, such as an excessive hæmorrhage or suppurative process, may also be important factors in inducing functional neuroses.

Of all the causes those connected with the male sexual organs have been credited with the most active ætiological rôle such as prostatitis, posterior urethritis, seminal vesiculitis, etc., and general disorders and habits such as gonorrhœa, syphilis and masturbation.

(b) **Predisposing factors.** A continued high atmospheric temperature with excess of humidity makes people in the tropics ease-loving

and much less hardy than those of the temperate climes. A little super-added physical or mental strain often brings about a nervous breakdown and makes a man physically unfit to cope with his environment. People working in the open spaces get easily tired owing to heat of the sun and cases are on record where many a people after long continued illnesses as malaria, kala-azar, etc., and apparently healthy, have succumbed to heatstroke.

Due to climatic influence in the tropics and to keep body temperature below the surroundings a large quantity of blood is regularly required to flow in the peripheral circulation especially in hot weather. People lose appetite in the hot weather, metabolism and ordinary physiological functions and biological processes are depressed lowering body vitality and making them an easy prey to nerve exhaustion. Again in hot weather, people are prone to remain indoors to protect themselves from hot blasts of air. The resulting ill ventilation with all its effects tells upon the health of the people. Anæmia and other diseases of the blood due to improper aeration of the blood-cells result. People use nets to prevent the biting of disease-producing mosquitoes and this is considered to be sleeping under unhygienic conditions leading to general depression of body vitality.

The social conditions of people living in the tropical countries contribute a great deal to the causation of symptoms of neurasthenia—

(a) **Heredity.** It accounts for a good number of cases. This has already been dealt with in discussing primary or congenital neurasthenia. Women are more prone to this type. If, as maintained by sexologists, marriage is an important factor to prevent neurasthenic symptoms in grown up unmarried girls, definite cases are on record where married, multiparous women suffer from neurasthenia without any other obvious discoverable causes. Other social conditions as early marriage, early and repeated pregnancies associated with ill-nutrition and strain and stress of life and other maladies make people of the tropics frequent subjects of neurasthenia.

(b) **Diet.** People in tropical climates live on a diet which can be hardly borne by those of temperate countries and so it is held by authorities of public health that such a quality of diet cooked with highly-spiced articles, mustard oil with its irritating allyl isothiocyanate, etc., is responsible for gastric troubles such as hyperchlorhydria, gastritis, peptic ulcers, etc. The digestion is enfeebled and delayed and is associated with atonic constipation and gastralgia is sometimes complained of. Hyperchlorhydria is sometimes observed and gastropnoxis is not infrequent. Meteorism, alternating constipation and diarrhoea, colicky pains due to defective intestinal digestion and the resulting fermentation are prominent features of the later stage. In these cases, auto-intoxication is an important feature.

(c) **Exercise.** That diet and exercise should go hand in hand is an old adage. Fat and forty-year-old Indians are often diabetics.

Visceroptosis and cases of prolapse-uteri in quite young Indian girls are the result of lack of proper exercise and such girls always suffer from vague symptoms of neurasthenia such as indigestion, attacks of abdominal pain (hypochondria) associated with various endocrine dysfunctions and particularly of the thyroid and adrenals. All these predisposing causes combined with toxins of acute and chronic illnesses characteristic of the tropics play an important rôle in the causation of neurasthenia.

(d) **General endocrine dysfunction.** The endocrine system may be thrown out of order, as a result of the patient suffering from some acute disease such as enteric fever, cholera, bacillary dysentery, small-pox, etc. Long-continued illness such as malaria, kala-azar, chronic genito-urinary diseases or absorption of the toxins arising from putrefactive changes in the gut may occasionally put an undue stress on the glands such as the thyroid and adrenals. That the ductless glands play an important rôle in the genesis of neurasthenia is probable. The thyroid and adrenals play an important part in oxidation and in protecting the body against auto-intoxication, and any condition which exhausts these organs must necessarily impair the general dynamism and lower the vascular tension, the underlying cause of neurasthenia in many cases. It must be clearly understood in this connection that cases classified formerly as neurasthenia are due to disorder of the internal secretions. In dysthyroidism there are recurrent states of neurasthenia and great prostration. Pituitary disorders too create symptoms of neurasthenia. Insufficiency of the adrenals also produces neurasthenia characterised by extreme asthenia, inability to think clearly, and as a rule associated with low blood pressure.

Diagnosis. Bennett (1918) was of opinion that there is practically always in true neurasthenia a long prodromal period, the pre-neurasthenic state, characterised by well-defined morbid manifestations indicative of aberrant functioning of the emotional centres. The immediate cause of this instability is the reaction of environment on the patient's mind. This state is not actual neurasthenia and may not develop into it, but neurasthenia is its culminating development. Neurasthenia is a definite syndrome and should not be confounded with the nervous asthenia resulting from abuse of stimulants, drugs or tobacco as being symptomatic of organic diseases. Neurasthenia should be clearly differentiated from obsessions, hysteria, melancholia and hypochondriasis. The heart and blood vessels are usually the first to reflect the central functional disturbance in neurasthenia.

Reviewing the innumerable factors responsible for bringing about the condition of neurasthenia, there is no doubt that it is a malady not without obvious causes. A proper diagnosis should be made, largely by a process of exclusion. All possible gross organic diseases are to be excluded and careful investigation is most essential regarding the daily life of the neurasthenic together with complete physical examination of

the subject. If this procedure is not adopted several diseases of the body and mind will be wrongly diagnosed as neurasthenia. Amongst them early phthisis with symptoms of indigestion, feeling of ill-being in an apparently healthy young man, diabetes, Addison's disease, disseminated sclerosis, cerebral tumour, cerebral arteriosclerosis and encephalitis lethargica, general paralysis of the insane and dementia præcox deserve special mention.

A line of demarcation should be drawn between real organic diseases and the functional disorders of the nervous system. Besides the diseases mentioned which simulate symptoms of neurasthenia there are many more which cannot be discussed here for want of space.

Treatment. The prognosis and the line of treatment depend chiefly on a right diagnosis of the cause of neurasthenia. Cases of secondary neurasthenia always make a complete recovery after removal of the primary causes and all that is needed is proper rest and treatment of those diseases. There may occur periods of improvement but relapses occur readily.

The treatment of cases of neurasthenia does not merely consist in the application of specific drugs against such diseases as are responsible for its development. Although the importance of such a procedure should always be recognised, general tonics such as phosphorus (glycerophosphate of iron, both organic and inorganic), arsenic (with all its synthetic preparations) and strychnine combined with nourishing and proper dieting, regular and graduated exercise and open-air life, rest mental and physical, distraction and removal of baneful influences as far as possible constitute the prominent features of the treatment.

The benefits of rest in the average case may be secured by spending four to six additional hours in bed, by retiring early and getting up late. Or, if it is convenient, a couple of hours' rest during the day may replace the morning hours of rest. Each phase of the non-pharmaceutical treatment must be regulated to suit the patient's means and strength. Travelling is always useful, changes of scene greatly tend to alter the morbid trend of the mind.

Isolation is beneficial when neurasthenia is accompanied by very marked symptoms of lowered nutrition and muscular weakness and when a prolonged rest in bed is insufficient to arrest emaciation. Over-feeding is sometimes, obligatory and

may be carried out by the addition of milk and eggs to an ordinary mixed diet between meals.

Gastric functions should be analysed and diet adjusted accordingly along with administration of dilute hydrochloric acid before meals where hypo- or anacidity is found. Any foci of infection present should be properly dealt with.

Women mostly suffer with a train of abdominal symptoms due to lack of tone of involuntary muscles of the various abdominal organs and such diseases are cecal stasis, prolapse of abdominal viscera and various other pelvic organic diseases. Patients with visceroptosis are very commonly met with complaining of vague abdominal pains. A skiagram always settles the diagnosis. The patient should be advised proper abdominal exercises, small but frequent dieting, a well-fitting abdominal belt and sometimes electrical treatment with sinusoidal current. Cases are on record which show that this line of treatment has cured many such neurasthenic patients. Chronic cecal stasis should be treated by regular abdominal massage and by drugs such as cascara, senna leaves or pods stewed with prunes, etc. Sometimes surgical measures are adopted to cure patients with neurasthenia. Removal of the appendix, fixation of the floating kidney, gastropexy and a few pelvic operations in females have been known to cure neurasthenic patients.

In cases of neurasthenia, resulting from sexual abuse, rest of function is essential. Local treatment, especially of the verumontanum has been widely advocated, but some believe that such treatment only acts by suggestion. Sexual neurasthenia is often ascribed to a definite pathological condition of the genito-urinary tract especially in the vicinity of the verumontanum but some authorities do not agree on the point. Electricity has been advocated by many. Static electricity, slowly interrupted faradic current or diathermy may be conveniently employed.

Hydrotherapy has also been highly recommended. Winternitz's method of cold pack along with the application of warmth (122°F. or 50°C.) over the epigastrium or the application of cold over the spine is credited with marked efficacy.

Sleep is favoured by taking a warm bath for ten minutes followed by a glass of hot milk just before retiring.

Medicines. Few medicines are of value; the elaborate process of nutritional repair, favoured by the aid of the above-mentioned procedures, renders drugs relatively unnecessary.

Neurasthenia is recognised to be a vasomotor neurosis, the prominent feature of which is relaxation of all arteries, due to exhaustion of the sympathetic centre and the resulting loss of propulsive power of the arterioles. The tissues thus become imperfectly oxygenated and nourished, hence mental torpor, habitual fatigue, adynamia and gastro-intestinal atony result. There are various functional disturbances associated but certain degree of hypothyroidism is always present. Hence small doses of desiccated thyroid is recommended by some, usually in combination with strychnine, and full amounts of an assimilable form of iron such as Blaud's pill. Strychnine is supposed to be almost a specific in neurasthenia. Doses should be gradually increased and excess of 6 mg (1/10 gr.) may be given in daily doses. Arsenic, iron and other tonics are often valuable. Of the glandular products, thyroid gland (Armour's) in 1 gr. doses (which equals 5 gm. of fresh gland) or pituitary (whole) 2 gr. three times a day are very efficient. Corpus luteum in large doses is sometimes very effective in women.

Laxatives are important to counteract the auto-intoxication. The intestine should be flushed with calomel and a saline purgative at the start. Later, cascara, rhubarb, or aloin are suitable. The endless complaints and fault-finding nature of neurasthenics are in most cases symptomatic. Psychotherapy is usually effective in such cases. Sympathy and consideration on the part of the attending physicians, always gain the patient's confidence and ensure his co-operation which is of primary importance in the curative measures instituted.

Under proper prophylactic measures and judicious treatment however, prognosis is usually favourable. The just merit of each individual case should be taken as the guide to treatment.

CHAPTER IV

POISONOUS ANIMALS

SNAKE VENOMS

The subject of snake venoms is of special interest in India. In a population of 373,000,000 at least 20,000 to 25,000 deaths occur every year from snake bites; the fatality rate being 35 to 40 per cent. The number of deaths from the same cause is likewise considerable in Burma, Indo-China, China, Australia, Africa, West Indies and Tropical America, but the exact rate in these areas cannot be estimated accurately. The temperate parts of the globe are far less severely affected. In Europe the only poisonous snake is a variety of a small pitless viper; its bite mostly produces local symptoms and is rarely fatal. The most dangerous species to man are found in the tropical regions of Asia and Malaysia. In India, during the last 30 years or so a great deal of attention has been directed towards the classification of different snakes, the study of the chemical and biochemical nature of their venoms, their toxicity and the preparations of antivenines. Interesting investigations have also been carried out in America, Japan, Australia and Germany on the neurotoxic and hæmolytic principles. In passing it may be mentioned here that the discordant results obtained by various observers are in all probability due to variation in the chemical composition and the relative proportions of the active principles present in different specimens of the venom.

Classification and Identification of snakes.

Most of the deaths reported from snake bite in India are from the bites of the Cobra (*Naja naja*), Indian Daboia (*Vipera russelii*) and Phooras (*Echis carinata*). The last in order come some varieties of Kraits which rarely bite, though their poison is very deadly.

The poisonous effect of a particular snake is dependent upon (1) the toxicity of the venom, (2) the possession of fangs, (3) the amount of venom present in each of the glands, and (4) the dose injected. The snakes possessing anterior fangs are only to be regarded as poisonous to man.

Wall (1913) classified all the snakes into three groups according

to the shape and situation of the teeth in the upper jaw, (1) *Aglypha*, these are harmless snakes having no poisonous fangs, (2) *Opisthoglypha*, these snakes have grooved fangs situated at the back of the upper jaw, (3) *Proteroglypha*, this group has specialised grooved fangs in the front of the upper jaw. The last is really the poisonous group since the fangs dig deep into the tissues during the act of biting.

In poisonous snakes the maxilla is very small, freely movable, the front tooth on each side is specialised by being large, grooved and canalculated to form a fang. On examination of the mouth, the prominent anterior fangs are seen projecting or lying folded on the roof of the mouth and covered with a fold of the *levator menti dentis* in which lie concealed the reserve fangs. The table below gives the chief characters of the different types of snakes.

How to recognise poisonous and non-poisonous snakes.

According to Cazaly (1914) the poisonous and non-poisonous snake can be differentiated as follows:—At first put the unknown snake into one of the four groups mentioned in the table below: Place the snake on its back and examine its belly. If there are no ventrals or only narrow ventrals, the snake falls into group I or II. The snakes in both these groups are non-poisonous and harmless. If on the other hand the ventrals are broad, the next step is to inspect its head. If it is scaly the animal belongs to group IV which includes all types of vipers. If the snake has broad ventrals and a shielded head, it falls into group III, which consists of both poisonous and non-poisonous types of cobras. If any doubt exists regarding a cobra, examine the scales on the upper lip. If the third supralabial scale touches the nasal shield and the eye, the specimen is not a cobra is a krait. There is usually a tendency to call all the small-sized snakes as kraits. Indian adult kraits are usually 2 to 3 ft. in length and may grow up to about 4 ft. The banded or Burmese kraits may reach nearly 6 ft. in length. The chief identification mark of a krait is a distinctly enlarged row of the vertebral scales along the middle line of the back; if these scales are of the same size as the other ones, then it is not a krait at all. The other features of the kraits are that there are usually cross bands, and their subcaudals are usually entire. Lastly, to make quite certain examine the scales on the lower lips. A krait has only 4 infralabial shields and the 4th one is the largest. The group IV of vipers is recognised by the head being covered with fine scales similar to those covering the whole body. The scales are usually of the saw type. A common Indian snake *Lycodon aulicus*, the bite of which is practically harmless, is often mistaken for a krait; it only evokes a transient local irritation. The pit vipers have a 'Loreal pit' situated between the nose and eyes. The vipers are characterised by a triangular head, vertically elliptical pupil and a short stumpy tail with a thick-set body. The maxillae are freely movable and each one carries a large anterior fang.

Table showing chief characteristics of the four groups of snakes in India

Group.	Dorsal surface.	Head.	Teeth.	Belly.	Particular features.	Remarks.
I	Covered with fine scales.	Shielded or scaly.	Fangs absent.	Covered with scales, no ventral plates	Entire body covered with scales only.	Usually olive green, brown or black in colour, harmless to man, found every where in India.
II	do.	do. Separate from the body.	do.	Transverse ventral plates do not extend completely across; several dorsal scales extend on either side of ventral	Head surmounted by a prominent snout.	Length 10 to 20 feet. Very stout. Varieties: pythons, boas, earth snakes and iridescent snakes. More or less harmless.
III (a) Cobra	do.	Covered with shield, with a hood	Fangs fixed, curving backward, canalculated	Broad, transverse shields stretch across ventral surface, last row of dorsal scales only seen when placed on the back.	Maxilla freely movable. Third supralabial shield touches the eyes and the nasal shield. Black spots on the whole body.	(a) The Cobra (<i>Naja naja</i>) (b) King Cobra or Hamadryad (<i>N. bungarus</i>). Majority in group III are poisonous and common in India and Burma.

Group.	Dorsal surface.	Head.	Teeth.	Belly.	Particular features.	REMARKS.
(b) Kraat	Distinctly enlarged middle row of scales along the vertebral line.	Covered with shield with head.	Fangs fixed, curving backward, canalculated. Shorter than that of cobra.	Broad, transverse shields stretch across ventral surface, last row of dorsal scales only seen when placed on the back.	Only 4 infralabials and the fourth one largest. Subcaudals are entire. Cross-bands on the whole body. Pit absent.	Very poisonous. Usually small size, Indian species up to 2-4 feet, Burman banded kraits up to 6 feet in length. (a) Common krait (<i>Bungarus caeruleus</i>). (b) Banded krait (<i>B. fasciatus</i>). Length 5-6 ft.
IV (a) Pitless viper	Scales.	Head triangular, fine scales similar to those on back.	Longer than that of cobra, up to 4", covered with levator vaginæ muscles.	do.	Covered with triple row of oval markings on the back. Tail stumpy. Eyes elliptical, maxillæ freely movable. Nostrils large.	Very common in Indian plains. Poisonous next to cobra. It is called <i>Vipera russelli</i> . Size up to 5½ feet.
1. Indian Daboia						
2. Indian Saw scaled viper	Saw type scales.	do	do.	do.	Undulating crescent markings on the back. Venom action only localised. Tail short.	Common in N. W. F. P., South India and Rajputana, etc. Called <i>Echis carinata</i> , <i>Phoosar</i> or Kuppur.
(b) Pit-vipers.	do.	do. Pupils vertical.	do.	do.	Loreal pit between the eyes and nostrils. No other species possess this pit.	Common green viper (<i>Lachesis gramineus</i>) Himalayan viper (<i>Ancistrodon himalayanus</i>).

The pharmacological action of snake venoms. The venom when fresh is a transparent and clear fluid. It is faintly acid in reaction and its consistency varies from that of water to that of the white of an egg. Cobra venom is a transparent, amber-coloured or almost colourless fluid having a specific gravity of 1.110. It is acid in reaction and slightly disagreeable in taste. The crotalus venom varies from a pale to an emerald green and orange or straw colour. It has no taste and its specific gravity varies from 1.030 to 1.044. The venom rapidly becomes alkaline in reaction on account of the disappearance of a volatile acid during decomposition. When dried under a bell jar on concentrated sulphuric acid or in the sun, it loses about 50 to 70 per cent. of water and is converted into a yellowish scaly mass and can be easily powdered. If kept in hermetically sealed ampoules and in a cool dark place it keeps its potency for a long time. The toxic principles of the venom reside in albumins which are thermostable, and a coagulable proteid which is thermolabile. The former is in excess in cobra venom and is associated with 'neurotoxin', and the latter is in excess in viper venom and is associated with 'hæmorrhagin'. The viperine venom contains another substance probably a cytolytic one releasing thrombokinase from platelets, etc., which causes intravascular clotting. As far as is known, the following substances mainly enter into the composition of the venom—fibrin ferments, proteolytic ferments, cytolsin acting upon the red cells, leucocytes, epithelial cells, nerve cells and agglutinins, and neurotoxin having a selective action on all the nerve tissue, especially on the respiratory and vasomotor centres. The toxic effects of different venoms are briefly stated in the table below :—

Class	Nervous system.	On blood and blood vessels.		
		Hæmolysis.	Coagulation.	Hæmorrhages.
Hydrophidæ (Sea snakes)	Paralysis of resp. centre & muscular system.	very slight.	slight reduction.	Nil.
Colubridæ (Cobras).	do.	moderate.	Nil.	Nil.
Viperinæ (True vipers)	Paralysis of vasomotor centre.	pronounced.	Intravascular clotting, in high concentration and in incoagulability in low concentration.	Very pronounced
Crotaline (Pit vipers)	do.	do.	Intravascular clotting less pronounced; coagulability pronounced.	do.

As regards the action of different venoms on man it has been observed that the neurotoxin in cobra venom has a special affinity for the respiratory centre and for the neighbouring ganglia of the 9th, 10th, 11th and 12th cranial nerves, and has a curare-like effect on the motor end plates of muscles. The krait neurotoxin has a selective action on the anterior horn cells of the spinal cord.

Phisalix and Pasteur (1928) noticed that animals vaccinated against rabies were refractory to the action of venom of the cobra and viper and *vice versa*, in other words the virus contained an antigen both for rabies and for the venoms. It has been further shown that the exposure of the venom of *Vipera aspis* to the ultraviolet rays does not diminish its virulence but increases it in certain cases. The ultraviolet rays however destroy the antirabic power of the venom. A temperature of 100°C, although destroys the toxin and the antivenomous properties of the viper venom, it does not produce any effect upon its rabicidal properties.

The venom of the Indian cobra. A large example of *Naja naja*, the Asiatic cobra, is six feet in length. The colouration of the typical form is yellowish to dark brown with a black and white spectacle-marking on the hood (seen when fully spread) and a black and white spot on either side of the lower surface of the hood. This form is more commonly found in Southern India and Ceylon. There are several varieties in India without hood markings.

Acton and Knowles (1914) found that an adult cobra of 4 feet 2 inches injects about 211.3 mgm. of the venom at a single bite, while the M. L. D. of cobra venom for a man of 60 kilo. is about 15 mgm causing death in three hours (see table). This shows that the cobra generally injects about 10 to 15 times the M. L. D. In the case of a common krait about 5 mgm. is injected at a single bite. The M. L. D. for monkeys is 0.15 mgm. and for a man it is estimated to be 1 mgm., it therefore injects about 5 to 10 times the M. L. D.

Chopra and Ishwariah (1931) investigated in detail the pharmacological action of the venom of the Indian cobra (*N. naja*) and reported that the M. L. D. of this venom varies with different species of animals. It is less toxic to frogs, cats and rats but fatal to dogs, rabbits and men. When injected intravenously the venom produces immediate fatal effects. If the dose is large, the animal dies within a few minutes from respiratory failure. The venom being colloidal in nature, its absorption is slow if injected hypodermically or intramuscularly and hence the symptoms are much delayed and death may be delayed from 4 to 24 hours. When given by the mouth the venom is not absorbed by the intact mucous membrane and does not produce any marked toxic effects. It has been shown that the venom is identical to the salivary secretion, and is a digestive enzyme. It does not affect the activity of the salivary, gastric and pancreatic secretions of man *in vitro*, though it slightly increases the muscular tone of the gastro-intestinal tract in cats and rabbits. The sublethal doses produce a small but persistent

Table showing M. L. D. for different types of snakes .

Snake	Approximate dose at a single and good bite, in mgm.	M.L.D. for rat, in mgm.	M.L.D. for monkey, in mgm.	Estimated fatal dose for man, in mgm.
Common Cobra (<i>Naia naia</i>)	211.3	0.12	2.4	15.0
King Cobra (<i>Naia bungarus</i>)	100.0	0.05	1.8	12.0
Common krait (<i>Bungarus candidus</i>)	5.4	0.20	0.15	1.0
Banded krait (<i>Bungarus fasciatus</i>)	42.9	0.10	1.5	10.0
Indian Daboia (<i>Vipera russellii</i>)	72.0	2.5	7.5	42.0
Phoorsa (<i>Echis carinatus</i>)	12.8	1.0	0.5	5.0
Green pit viper (<i>Lachesis gramineus</i>)	14.1	0.5	16.0	100.0

rise in the blood pressure in experimental animals. The rise is not due to the stimulant action in the accelerator mechanism of the heart or due to the action on the myocardium. In experimental animals no concentration could produce any definite stimulation or reviving effect on the failing heart. Large doses appear to act directly on the heart muscle and produce depression followed by cessation of its movements. The rise of blood pressure appears to be due to the temporary stimulation of the vasomotor centres. The subsequent marked fall of the blood pressure is due to late paralysis of the vasomotor centres. The main action of the venom is on the respiratory centre which is initially stimulated followed by paralysis. Histopathological studies of the brains of cobra-poisoned mice, as studied by Scharenko, showed that the toxin paralysed the vasomotors followed by a local stasis and subsequent corresponding necrosis.

It has no action on the motor end-plates of the diaphragm and other muscles involved in the mechanism of respiration. The action of the venom is exclusively on the nervous mechanism and this was demonstrated by Chopra and Chowhan (1931) by a detailed study of its action on protozoa. It was observed that the venom of the Indian cobra is toxic to protozoa. The paralysis of the movements of *P. caudatum*, which appears to possess a rudimentary neuro-motor apparatus, by cobra venom is confirmatory evidence of its selective action on this organ. It was further shown by them (1932) that the venom of Russell's viper, which is poor in neurotoxic principles, does not produce any effect on the activity of the movements of *P. caudatum*. The action of this venom is mainly on the endothelial cells of the vascular system and as these protozoa have no organised vascular system, they are immune to the toxic action of viper venom, while the animals which have a well-developed vascular system are severely affected by this venom.

The venoms of the Indian daboia and other vipers. These vipers are considered to be next to cobra in the order of their toxic action. The most important Indian pitless viper, called the Daboia or *Vipera russelli* is locally known as *uloobora* or *tic-polonga*. The other important viper is *Echis carinata* also known as the saw-scaled viper, Phooras or Kupper. The daboia is found in all parts of India, Ceylon, Burma, Siam, Sumatra and Java, whilst the saw-scaled viper is frequently met with in the N. W. F. P., Sind, Rajputana, Central India, Madras and Ceylon. Vipers (commonly called adders) are found in various conditions, in open woods where there are slopes and gullies exposed to the sun, on heaths and moors. Heaps of loose stones or tumbled walls are favourite prowling places and hunting grounds for food. Like the American rattle snakes and copper head, they prowl into the farms during the late summer, when the grain has ripened, in search of small rodents and are often discovered under sheaves or thrash piles. In the mountains they occur up to elevations of at least five thousand feet. They return to specific places to hibernate, but in congregating at their dens in the autumn are not so easily seen as they hide under the early fall of leaves where their body hue and pattern blend with the ground. The small size of the viper enables it to work its way through comparatively small holes.

The venom of the Indian daboia is a clear orange coloured oily fluid, having a specific gravity of 1.077 and when dried it yields orange coloured scales or masses. There has been considerable doubt regarding the action of the viper venom. Wall (1863) and Cunningham (1896) were pioneers to study the action of cobra and viper venoms. Mitchell and Reichert (1896) showed that the intense local irritant action and the sense of burning pain felt after the bite of a viper are due to the large quantity of globulin (as much as 25 per cent.) present in it, while the albumoses, which is responsible for the nervous symptoms,

is present only in very small quantities. Viper bites lead to severe pain, abscesses, gangrene and often multiple hæmorrhages and later ascending paralysis of the central nervous system. Lamb and Hanna (1903) made some observations on the properties of the Indian Daboia venom. Rogers (1904) working on the antidotes of colubrine and viperine venoms recorded that a small dose of Russell's viper venom intravenously could kill by a rapid fall of the blood pressure without any intravascular clotting, but with a loss of coagulability. This condition could always be produced by injecting a sublethal dose while a large lethal dose produced a fatal circulatory failure. He proved, by cutting the spinal cord, and by direct observations on the portal circulation, that the essential cause of death was paralysis of the vasomotor centre, the heart continuing to beat to the end. The African puff adder, the American rattle snake and the Indian pit vipers, all produce death in the same manner so that vasomotor paralysis is the main action of viper venoms and, in addition, there is a hæmorrhagic effect which is most marked in the case of the rattle snakes. Acton and Knowles (1914) showed that daboia venom contains a hæmorrhagin which destroys the endothelial cell lining of the finer blood vessels and consequently gives rise to ecchymosis and extravasation of blood, the convulsions seen early in viperine poisoning being due to small hæmorrhages in the cerebral cortex; a *cytolysin* which dissolves the red blood corpuscles releasing a fibrin ferment (*thrombase*) which causes intravascular clotting, pulmonary embolism and death from asphyxia. The slow and delayed symptoms after the venom is injected are probably due to low dosage. The fatal dose for a monkey of 25 kilo. weight is 7.5 mgm. and for man the M. L. D. is 42 mgm., death occurring in 24 hours. The average dose given at a single bite is about 72 mgm., which is about double the minimal lethal dose. Crimmens (1931) stated that the diamond black Rattlesnake of Texas may discharge 9 to 40 lethal doses of the venom at one bite. In the case of the *Echis* the M. L. D. for a monkey is 0.5 mgm. and for a man is 5.0 mgm. and the approximate dose of the venom injected at a single bite is about 12.3 mgm. Here also the snake injects almost double the fatal dose. Chopra and Chowhan (1934) investigated the pharmacological action of the venom of the Russell's viper, and found that the hæmorrhagic phenomena appear at the outset of poisoning and are very extensive in character. Death is preceded by spasmodic and irregular respiration, convulsions and asphyxia indicating the involvement of the vagal centre owing to deficient blood supply. In all post-mortem examinations recorded, the lungs show symptoms of asphyxia, petechial hæmorrhages and infarctions. The right side of the heart is full of dark blood and the left side is empty and tonically contracted; the blood is not coagulated. In animals which have died of daboia poison the kidneys show inflammation, mottling of the cortex and extensive hæmorrhages. The serous cavities such as the pericardium, the pleura and the peri-

toneum are full of sanguinous fluid, probably produced by injury to the delicate endothelial cells of the capillaries leading to excessive leakage of the blood.

The daboia venom has a marked tendency to produce thrombosis and gangrene at the site of the bite and death is due to secondary shock. The systemic blood vessels, especially the peripheral ones, are found to be contracted and those of the splanchnic area are widely dilated as in histamine shock. That the nervous centres are not much affected is shown by the fact that in decerebrated animals exactly the same results are produced. If the action is prolonged, these measures are of no avail since the normal relative permeability of the vessel walls to the protein constituents of the blood is lost. The capillary leakage goes on to such an extent that anything injected leaks out of the vessels. The symptoms of shock in daboia poisoning are not due to reflex impulses, but are due to the local dilatation of the capillaries of the splanchnic area. The paralytic action of the venom seems to be confined to the capillaries only and is similar to histamine.

In the case of *Lachesis*, Vellard and Vianna (1932) found that intramuscular and subcutaneous injections in dogs produce an initial incoagulability, due to rapid destruction of fibrinogen and of the complement by the protease of the venom, subsequently there is absence of formation of thrombin due to the action of the venom on the hepatic cells and hæmolysins are also increased. After intravenous injection there is at first intravenous clotting, followed by incoagulability of the blood in about five minutes. It was further shown that while the venoms of *Lachesis* and *Trimeresurus* are anticomplementary, the cobra venom has less and slower anti-complementary action and *Crotalus* has no action on the complements at all. A certain incubation period precedes the anti-complementary action. Malcolm, Smith and Hindle found that the M. L. D. (for mice) of the venoms of the pit viper (*Trimeresurus sumatranus*) and *T. vagleri* to be 0.5 mgm. and 2.45 mgm. per kilo. body weight, and that of the sea snake (*Latecauda colubrina*) to be 0.118 mgm. but they doubt that the total yield of the venom for any of these three species is sufficient to render the bite dangerous to a healthy adult person.

The mechanism of the bite. There are four distinct phases when a poisonous snake bites.

(1) *The strike.* In this phase the snake throws itself forward with great rapidity and violence, the distance covered not generally exceeding one-third of its length. The vipers strike with greater velocity than the colubrids, some of which—especially the hooded species—raise the head from the ground, so compensating to some extent for the limited mobility of the fangs.

(2) *Opening of the mouth and elevation of the fangs.* Most poisonous snakes commence the strike with closed jaws, but as the head approaches the victim the mandibles are depressed by a rapid contrac-

tion of the digastric, cervico-mandibular and vertebro-mandibular muscles and simultaneously the fangs are elevated or rotated forward by the forward swing of the pterygo-palatine-transverse arch produced by the contraction of the spheno- and parieto-ptyergoid muscles. The fangs of the colubridae are invariably grooved and are generally shorter than those of the viper, and their capacity for forward rotation is much more limited.

(3) *Closure of the mouth and the injection of the venom.* Closure of the jaws follows, a result brought about by the simultaneous contraction of the anterior, middle and posterior temporal muscles which strongly elevate the mandibles. In the colubrids the venom gland is also compressed by the superior and inferior portions of the anterior temporal muscles, producing torsion of its capsule with the expulsion of venom from the gland along the duct, the papilla of which becomes approximated to the groove at the base of the fang. Fixation of the jaw is important in effective biting by colubrides, as emphasized by Acton and Knowles. In the vipers there is an entirely different anatomical arrangement of muscles acting on the venom gland; expulsion of its contents is instantaneous and independent of fixation of the lower jaw.

(4) *Retraction of the fangs.* Immediately following the insertion of the fangs, and actually accompanying the discharge of venom, contraction of the retractor muscles (the parieto- and spheno-palatine and the internal and external pterygoids) which operate on the pterygo-palatine-transverse arch occurs, dragging the elevated fangs downwards and backwards through the tissues.

The pathology and the character of the wound. The shape and the severity of the wound depend upon the vascularity of the area and the anger with which the snake attacks. The wound may be absolutely blind if the animal happens to bite through thick clothes, but if through the bare skin the puncture resembles that made by a large hypodermic needle. There are generally two punctures of the fangs $\frac{3}{8}$ to 1 inch apart.

Pain. Immediately after the bite pain is usually local, severe and scalding in character. Later, the pain may increase and radiate along the whole length of the limb followed by numbness and heaviness of the bitten limb.

Swelling. It usually occurs within 10 to 20 minutes after the bite and is intense, brawny and indurated in character. The swelling is very painful, does not pit on pressure and rapidly extends higher up along the body.

Discoloration. The skin may become bluish black in colour due to the action of the venom on the haemoglobin and may end in blisters, abscess and gangrene.

In the act of the bite the fangs penetrate the tissues and the venom is injected synergistically. The snake grips the tissues tightly in its

mouth, the subtemporal muscles contract with great force, the levator vagina of the palate is elevated and the venom glands are squeezed. The venom finds its passage along the grooves of the fangs into the wound. It is almost always injected into the subcutaneous tissues, with a considerable degree of torsion and compression. In cases where hands and feet are involved the teeth may even penetrate the deeper tissues and tendon sheaths. In the case of the Death Adder, the fangs are very long, more curved and rotated forward. The bite here is much more powerful due to the highly developed temporal muscles, hence the venom is deposited much deeper into the tissues. The injected venom is usually very concentrated and irritant and is not absorbed unchanged. This irritant part of the venom induces engorgement of the perilymphatic spaces and later on congestion of the tissues and veins which renders the part more suitable for absorption of the venom. The venom passes from the perilymphatic spaces into the lymphatic vessels and then makes its way into the general circulation.

Symptoms produced. The Indian Commission on snake bites in (1886) estimated that the average lapse of time between the infliction of a bite and the cessation of the respiratory function varies from 10 minutes to one hour (average 42 minutes), without artificial respiration. In the case of the Russell's viper death takes place in 2 to 7 days usually due to paralysis of the vasomotor centre and circulatory failure. Death occurs from secondary shock, while in the case of *Echis carinata* death is due to multiple hæmorrhages and consequent failure of the circulation and it may be still more prolonged.

(a) *The cobra and the krait.* The local symptoms consist primarily of pain at the site of the bite, radiating along the limb and later followed by œdema, paresis and numbness. As the venom is absorbed, partial paralysis of the limb and peculiar tremors occur all over the body; incoordination in speech, ptosis, drooping of the head, collapse, giddiness, reeling sensation, staggering gait, complete paralysis of all the voluntary muscles and blindness are produced. The breathing may become shallow and rapid and later diaphragmatic in character and may end in asphyxia with convulsive seizure. There is profuse salivation followed by paralysis of the tongue and the larynx. There may be obvious dysarthria often vomiting and involuntary passage of urine and fæces before cessation of respiration. The pupils remain active to light up to the end. The heart continues to beat for a much longer time after the stoppage of respiration. The krait of Northern India is one of the most deadly snakes. It has also been observed that the patients lose the taste for powdered chillies, raw onions and bitter neem leaves after a cobra bite. The symptoms produced are similar to those produced by the cobra venom but there are no convulsions. The symptoms produced by the bite of the Australian Colubrids are often not so severe as those of the Indian. There is a

feeling of faintness and irresistible desire to sleep, which is soon followed by paresis of legs, vomiting and cardiac paralysis. The pupils are widely dilated and are insensible to light. Should the patient survive the coma, the recovery is complete and no sequelæ follow.

(b) *The Russell's viper and the echis carinata.* The local symptoms are more prominent and severe in character and the victim feels as if a live coal is placed on his skin. He may even scream with the intensity of the pain. There is marked ecchymosis and persistent oozing of the blood from the site of the punctures and it is proportionately more profuse as compared to the depth of the wound inflicted. There is a marked fall of the blood pressure, small thready pulse, collapse, nausea, vomiting, widely dilated pupils which are insensitive to light. The loss of consciousness is more or less complete, from which temporary recovery sometimes occurs. Should the effect of the diffused toxins wear off, the local condition of the wound becomes aggravated. In severe poisoning convulsions set in in due course and death ensues from failure of the circulation. The post-mortem examination reveals congestion of the meninges and the lungs are full of fluid blood. On incising the bitten area clotting and hæmolysis of blood are seen which give the appearance of a red-currant jelly to the tissues. In delayed and less poisonous cases, blisters, abscesses, gangrene and secondary bacterial infection may occur. Multiple hæmorrhages, extensive petechial spots, epistaxis, hæmaturia, hæmoptysis, subconjunctival hæmorrhages and purpura are not uncommon.

Treatment. From time immemorial snake charmers all over the world have claimed the ability of overpowering snakes. They allege that they possess specific remedies against the poisons either in the form of charms or organic drug substances, sometimes obtained from the body of the snake itself which possess the power of extracting the poison out of the wound. The indigenous medicine in India has a long list of drugs claimed to possess specific antidotal properties against snake poison. Mhaskar and Caius (1931) tested about 300 of such reputed remedies, but none of these proved effective. The author has received a large number of preparations and secret remedies consisting of leaves, powders, pills, snuffs and eye salves, which are claimed to be effective remedies against snake bite, but they fail to neutralise or counteract the effect of the venom in experimental animals. The methods of administration recommended for these cures appear to be rationally unsound as it is highly improbable that the rapidly acting venom will be neutralised

by giving the drug by the mouth or application to the mucous membrane of the nose and conjunctiva or the skin. The venom of most of the snakes when injected intramuscularly is absorbed into the general circulation within 20 to 30 minutes and within a few minutes by the intravenous route. Most of the venoms have a selective action on the vital centres and fatal effects occur so rapidly that the patient is dead before any help is possible. It follows, therefore, that to be effective at all, the treatment should be vigorously and promptly applied and it is only in the case of locally acting and slowly absorbed venoms that such methods could be of any use.

On a patient being brought for treatment for snake bite, it should be ascertained whether the snake was seen or killed and identified. In this connection it is necessary to find out, (a) has the snake actually bitten and (b) was the snake a poisonous one. The first thing to do is to tie a proximal ligature on the limb and then to examine the area of the supposed bite. If there are no fang marks and no venom on the skin then obviously there is no danger, but fang marks on the skin or venom on the mucous membrane or on the skin with scratches may be dangerous. If the snake is available examine its mouth for the typical poison fangs in the anterior part of the upper jaw; also see if the head has the shape of an arrow as occurs in vipers. If the snake is found to be a non-poisonous one, the patient may still be suffering from acute, and even fatal shock due to fright, but an assurance that the bite was not dangerous, and simple treatment for shock, will always rapidly allay the symptoms.

If the snake has not been accurately observed or killed, the site of the bite should be closely examined for signs of the typical two punctures of the fangs a short distance apart, but it should be remembered that occasionally only one fang may have penetrated the skin, in which case the dose injected is likely to be a small one. If some time has elapsed after the bite, local swelling due to hæmorrhagic effusion will be present, and this is likely to be greater in viperine than in colubrine venoms, but on incising the bitten area some effusion will be evident within a few minutes after the bite. In any case,

treatment should be applied at once without waiting for symptoms of poisoning to appear, as by delay the chance of saving the patient is likely to be lost. When dealing with a case of bite from a poisonous snake, efforts should be directed firstly to prevent absorption of the poison, and secondly to neutralise as far as possible its toxic effects. Thus ligature, burning and suction of the wound are some of the very antique remedies which have been practised in India for quite a long time and number of other schemes have been practised.

The chicken method is used in some parts of India. Young chickens are obtained, their tail feathers are pulled off and the rectal portion of the tail is scarified or made raw with a sharp instrument and applied locally on the bitten and scarified wound. After being in contact with the wound for a few minutes the chicken is said to drop dead; another chicken is likewise applied and the process is continued till the chickens cease to die. The raw rectal surface of the chicken is believed to absorb the poison from the wound. This method might be of value where the poison remains localised and is slow in action as in cases of *lachesis* and *echis*. The cock's flesh while still warm has also been applied to neutralise the venoms of snakes; chickens' brains have been made use of for similar purpose. The fresh flesh of pigeons, swallows, burnt feet of fowls, and various fantastic things are alleged to be good against the snake bites. All these claims have been found to be baseless.

Snake poisoning consists in the hypodermic or intramuscular injection of a series of poisonous principles which act chiefly upon the nervous and the circulatory systems. Moreover the virulence of the poison depends upon the quantity of the venom injected and the size of the animal. The same quantity of the poison will thus have a more serious effect upon a child than upon an adult. The absorption of the venom depends upon the depth at which the venom has been lodged during the act of the bite and also depends upon the vascularity of the area bitten. Wounds are dangerous if near the face, neck, upper arm, trunk and thigh, and less dangerous if is on the toes of the feet or fingers. The smaller the quantity of the poison introduced into the circulation, the milder the symptoms. The first indication for treatment is therefore to prevent the passage of the poison as far as possible into the general circulation. The success of this procedure depends on the proper identification

of the snake and immediate application of first aid. In case of non-poisonous snakes the bitten area may be simply cleaned and treated aseptically.

The treatment of snake bite has been divided by Metcalfe (1927) into:—(a) Preventing the passage of snake poison into the general circulation, (b) neutralising the venom at the site of the bite, (c) neutralising the venom that has been absorbed into the general circulation by specific antiserum treatment, and (d) the treatment of the special symptoms and secondary complications.

The prevention of the passage of the poison into the general circulation. The methods consist in application of a ligature, incision of the wound, cauterisation and suction of the venom from the site of the wound.

1. *Ligature.* By ligature is meant the application of an elastic and a tight binder between the seat of the bite and the heart so that absorption of the venom into the general circulation is prevented and time for the use of local and general remedies is gained. This method was first used by Kemfer and later by Fontana (1781) who published his work "Traite sur la venin de la vipere" in Florence. Continued and intermittent ligatures have been advocated. In the latter the cord is loosened for a few minutes from time to time, careful watch being kept for the appearance of any constitutional symptoms, the onset of which calls for tightening of the ligature again. It has been shown that 6 or 10 times the fatal dose of the venom of the black snake (*Pseudechis porphyriacus*) could be injected into the legs of a rabbit without fatal results, if an elastic ligature is applied immediately after the injection of the venom; the ligature in such cases was tight enough to obliterate the circulation for about 20 minutes. On incising the bitten area, the blood and lymph were found to be clotted at the site showing that the poison is thus temporarily locked up and could only be absorbed slowly. In the case of cobra and krait venoms which contain no fibrin ferment, the ligature only delays the absorption of the venom as long as it is on and thus only prolongs the death interval. In the case of saw-scaled viper and the Russell's viper, where the venoms contain a

greater proportion of the fibrin ferment and a thrombase, the ligature helps in fixing the venom locally by producing thrombosis and thus greatly reducing the absorption rate of the venom. In case of lachesis, it was shown in Brazil that the ligature is not indicated as it produced gangrene at the site of the bite.

The method of application of a ligature. The binder should always be applied to the limb possessing a single bone, *e.g.*, the upper arm and the thigh and not on the forearm, calf, wrist or ankle which possess more than one bone and consequently the deeply seated interosseous blood vessels between them cannot be completely compressed by the help of a tight binder. The bandage should be applied within 10 minutes of the bite and it should be tight enough to obstruct the lymphatic and venous circulation, but it should not obliterate the arterial pulse. If a rubber tourniquet is not available a thick string, an elastic rubber tubing, belt, *dhoti* (loin cloth), turban or even a waist band may serve the purpose. The bandage can be tightened by inserting a piece of stick between the ligature and the limb, and twisting it on the ligature in a corkscrew manner; when the ligature is adequately tight the stick is kept in place by inserting one end underneath the ligature. It is loosened after about half an hour to allow the fresh blood to enter it and when the parts become pink the binder is tightened again. This procedure should be carried on every quarter of an hour so as to avoid serious damage to the tissues by prolonged local anoxæmia. After the first aid treatment, the ligature should be loosened more frequently and for longer intervals and if no cardiac symptoms appear it may be safely discarded.

The ligature is obviously made for delaying the passage of the venom into the circulation and thus extending the precious time for other active measures. *Effective ligature must remain the first and the foremost step in the treatment of snake bite.*

2. *Incision.* The second form of local treatment of value is the immediate and free incision into the site of the bite and its neighbourhood or after the application of the ligature in order

to let out the poison and to prevent the further absorption of the venom into the tissues. The skin and the subcutaneous tissues around the bitten area including the punctures of the fangs should be incised longitudinally along the muscle fibres and never across it. The incision is made in two stages:—

(a) The primary incision. It consists of cutting $1/8$ th to $1/4$ th of an inch, *i.e.*, as deep as the puncture of the fangs and is crucial in shape. Care should be taken to avoid big vessels or nerves. The effusion of the blood from the wound should be aided by squeezing the wound and by applying suction. (b) Secondary incision. After the primary incision and suction the wound may be further deepened to the subcutaneous tissues, *i.e.*, about $\frac{1}{4}$ to $\frac{1}{2}$ inch deep extending as far as the swollen margin. If the bitten part is a limb the incision should be circular, running all around the limb in the form of a 'bracelet'. Two such bracelet incisions about one inch apart should be made proximal to the wound. When the surface is flat as the back of the trunk, the incision should encircle the bitten and the swollen area. The secondary incision should be along the distal margin of the swelling and the suction should be continued for some time. If the swelling still increases, make another incision along the distal end of the fresh swelling and continue suction, for it is in the distal parts of the swollen area that the venom is more dilute and therefore is more likely to be absorbed into the circulation.

3. *Suction of the venom.* The sucking of the wound has been recommended by Celsus, but it should only be done by the mouth if there are no ulcers on the gums, palate, tongue, etc. The ligature and the incision must be supplemented by suction. The mouth is first rinsed with oil or warm *ghee* (clarified butter) and the wound sucked and spat out. The vacuum cups or suction apparatus have proved to be far more efficient than the suction by the mouth. A simple emergency suction apparatus can be improvised by attaching a rubber bulb to a glass funnel. The breast pump or cupping glasses also serve the purpose. Jackson and Dudley (1928) demonstrated experimentally that the venom can be removed from the tissues by the method of incision and suction. Experimental animals

after receiving as high as 4 M.L.D. of the venom could be saved by this method if suction was applied within an hour of the injection. The fluid sucked out contains the venom in solution and is highly toxic if reinjected into another animal and it can be neutralised with antivenom sera. The suction is repeated after half an hour. In the beginning the sucked out blood is thick, dark and semiclotting in condition, but subsequently it changes its appearance to a bright red colour due to hæmolysis and dilution with lymph.

4. *Burning and cauterisation of the bitten area.* This drastic procedure has sometimes been used. A burning coal or a red hot iron is applied immediately to the bitten area. Strong alkalis, acids such as nitric, sulphuric and carbolic, silver nitrate or crystals of potassium bichromate have also been used as escharotics. The disadvantage of this method is that as the burning only acts to a certain depth, absorption of the venom from the deeper layers cannot be prevented.

5. *Amputation.* This is another drastic treatment, but if done in proper time life may be saved. It is the best remedy, especially in viper bite. It is not indicated in cases of lachesis and echis bites where the mortality is very low, and its value is doubtful for cobra bite as the poison reaches the circulation within 8 to 10 minutes. It is useful in cases of bites of fingers and toes and when the patient is seen within ten minutes of the bite. Amputation is usually done by the patient himself as the cases are seen rather late for medical aid.

6. *Local venesection.* Kellaway (1920) demonstrated experimentally that venesection is of value in case of poisoning from the death adder and tiger snakes and can afford protection from a dose of one to one and a half times the lethal dose. It may be carried out within an hour or two of the bite before the ligature is removed. The idea is to wash out the parts with the patient's own blood. A second ligature, tight enough to obstruct the venous return, but not the arterial flow, is placed in position immediately distal to the arterial ligatures. An incision is made into one of the veins draining the bitten area and a succession of small blood-lettings from the vein is carried out by lifting the arterial ligature for a minute or two and

leaving the venous ligature in position. This treatment is quite useful, particularly where antivenene is not available. In an adult a pint and a half of the blood can be removed and if necessary replaced by transfusion or by giving an intravenous injection of a large quantity of gum in saline solution.

Neutralising and fixing the venom at the site of bite. It is clear that it is far more important and practical to destroy and neutralise the venom at the site of the bite before a lethal dose has been absorbed into the general circulation. Moreover, if less than a fatal dose has been absorbed before the patient comes under treatment, the destruction of the greater part of the remaining unabsorbed venom may turn the scale. The destruction of the venom locally is important in view of the uncertainty of the antivenene treatment, the amount of antivenene available to completely neutralise the large dose of the venom injected by a bite and the availability of an apparatus for intravenous injection. Cobra venom is absorbed quickly but in case of viper bite one ampoule of the serum should be injected locally at the site of the bite, and half an ampoule a little above the wound and below the ligature.

1. *Potassium or zinc permanganate.* About 200 chemical reagents have been tested, but their value in actual practice is limited. These remedies act by causing local coagulation and necrosis, thus destroying both the venom and tissues. The neutralising value of a chemical is greater when it comes in direct contact with large quantities of the venom and in high concentration. Chemicals are more suited for viperine than colubrine venoms.

Experiments by Brunton and Fayrer to prove that potassium permanganate oxidises the venom in the tissue were inconclusive, but Rogers (1914) showed that three to five times the lethal dose of venom of cobra or Russell's viper could be reduced to below the lethal limit by the application of the permanganate crystals treatment.

Acton and Knowles (1914) and Bannerman (1914) showed by *in vitro* and *in vivo* experiments that potassium permanganate has a marked action in destroying and fixing different venoms. The efficacy of this treatment depends upon the time and the mode of application. Wada (1917) showed that if potassium permanganate was injected within 7 hours of the bite, it neutralised the power of the venom by oxidising and fixing it locally. Unfortunately cases of snake bite usually occur in places where the victim is far from such aid and it was for such contingencies that Lauder Brunton devised his snake bite

lancet with a sharp blade at one end and a receptacle to contain potassium permanganate at the other end. The method advised was to cut open the bitten area and to rub in the crystals of the permanganate into the wound. After application of a ligature and the incision of the wound, a freshly prepared 1 to 2 per cent. solution of potassium permanganate should be forcibly injected with a Record syringe into and around the wound at various points until the solution begins to ooze out of the wound. The needle should penetrate at least $\frac{1}{2}$ inch deep into the tissues. The limb must be kept elevated and fomented with a hot and strong (3 to 5 per cent.) solution of potassium permanganate. The tourniquet should be kept in place as long as necessary, but not more than quarter of an hour so as to avoid necrosis of the area. Ten to twenty c.cm. of 1 per cent. solution can be injected into the bitten area. It is not always practicable to incise the parts with a lancet and rub the dry crystals of the potassium permanganate locally into the wound. The American authorities on the other hand do not recommend the local application of potassium permanganate, because they consider that it is toxic to the tissues and possesses no antidotal value.

2. *Gold chloride.* The use of gold chloride solution was suggested by Cunningham more than 3 decades ago, and later by Calmette and more recently Acton and Knowles advocated its use. One to five per cent. solution of this preparation can be injected subcutaneously around the site of the bite. Sealed ampoules of 15 gr. of gold chloride crystals are available in the market. The whole quantity should be dissolved in 20 c.cm. of sterile saline solution; this approximately gives a concentration of 5 per cent. The value of this treatment depends on the early administration and thorough diffusion of the bitten area before the venom is absorbed into the circulation. The salts of gold and permanganate should not be injected intravenously as they are both poisonous and ineffective by that method. Locally, extensive necrosis occurs after the injections. It has been observed that the use of ox-bile as a solvent improves the action of a weak solution of gold chloride and the permanganate. The local injection of gold chloride is considered superior to potassium permanganate but the former produces necrosis of the tissues.

3. *Dihydrochloride of palladium.* It is said to have proved more efficacious than gold chloride under experimental conditions.

4. *Calcium chloride.* A 2 per cent. solution can be injected locally and intravenously. It is said to be useful in preventing hæmolytic and aids the healing process; it is indicated in cases of *echis* and *lachesis* bites.

5. *Hydrogen peroxide.* It has been shown that injections of 1 c.cm. of hydrogen peroxide solution within 9 hours of the bite can oxidise about 5 mgm., i.e., 1.7 times the M. L. D. of the *Ancistrodon*

per kilo. weight of a rabbit. Its action is similar to that of potassium permanganate.

Artificial respiration. This is of value in colubrine poisoning if complete respiratory paralysis has not yet supervened. With the employment of artificial respiration, life has been prolonged as long as 30 hours after cobra bite. Artificial respiration should be kept up as long as the heart goes on beating. If the respiration fails, the administration of oxygen or carbon dioxide should be tried ; the latter gas can be given by making the patient breathe in and out of a bag thus increasing the carbon dioxide intake. In case of viperine poisoning, where death is due to cardiac failure and secondary hæmorrhages artificial respiration is useless.

Antivenene or specific therapy. The first scientific attempt to produce an artificial immunity was made by Sewell in 1887 in pigeons, when by small repeated injections he raised their resistance so high that they could resist 10 times the lethal dose of the venom of a crotaline snake. In 1892 Calmette showed that by repeated inoculation of venom heated to 80°C., a certain amount of resistance could be developed in animals. He also demonstrated that an antitoxic serum against cobra venom could be prepared by repeated injections of gradually increasing quantities of venom into horses and Fraser soon after independently arrived at a similar conclusion. Martin and Lamb showed that antivenene has a specific action against the venom employed for immunising the animal. Nuttall (1904) put forward the hypothesis that antivenene is of the nature of a precipitin serum and acts by forming a precipitate with the specific venom. Noguchi and Madsen succeeded in producing antisera by immunising horses with venom after the toxophorous group of the molecule has been destroyed, capable of neutralising the hæmorrhagin of the crotalus venom. The anticobra serum supplied by Calmette had some power of neutralising the venom of sea snakes, the king cobra and the common krait, but not that of banded krait, which has a partial viperine action. Kellaway (1931) believes that active immunity against snake venom is often not so exclusively specific as was once supposed, the high resistance of animals immunised to one

species of venom to other species of allied venoms being due to the similarity of venom in toxic constituents and to the close serological relation of the snakes.

Antivenene in India is prepared at Kasauli with the venoms collected at the Haffkine Institute, Bombay, in the form of Lamb's mixed cobra and Russell's viper antivenene. Experimental batches of pure echis antivenene have been prepared at the Haffkine Institute and at Kasauli and are effective. The former preparation is reported to be strictly specific for cobra and daboia venom but its efficacy also extends to the poisons of the closely allied species. The Pasteur Institute, Paris, prepares three antisera against the venoms of different snakes. These are (1) ER for European snakes, (2) AN for African snakes (*colubridæ* and *viperidæ*), (3) AO for West and Equatorial African snakes (*bitis* and *cepedon*), (4) C for the *Naja* snakes of India and Egypt. In Siam where cobras are particularly numerous, the Bangkok Pasteur Institute maintains a large establishment for manufacturing antivenene. The institute here is similar in its organisation and surroundings to the Butantan Institute of Serum Therapy in Sao Paulo maintained by the Brazilian government. This institute issues a univalent serum against the venom of the rattle snake and a multivalent serum against the bites by the central American snakes. The antivenene institute of South America has perfected a polyvalent serum for the bites of the rattle snake, copper head and moccasin. Monovalent, bivalent, or polyvalent antivenenes are now available for snake-bite cases in Europe, India, Africa, Japan, Java and Australia, as well as in the United States, Brazil, the Argentine and Central America.

The antivenene remains thermostable at 60°C. for five minutes, but is completely destroyed when the temperature is raised to 65°C. or above due to coagulation of proteins.

Detoxication of venom. The great toxicity of ophidian venoms has made the production of specific high titre antivenenes from horses a prolonged, hazardous and decidedly expensive affair so that any such process as detoxication of venom with simultaneous preservation of its antigenic properties becomes a matter of great practical importance to countries interested in the manufacture of antivenenes on a

large scale Grasset and Zontendyk (1933) of the South African Institute of Medical Research have done a good deal of work on the detoxication of snake venoms. Bile, colganal and formalin detoxicate the venom. The detoxicated venoms are subsequently used for immunisation experiments in animals. Maitra and Mallik (1932) observed that the contact of hepatic lipoids with daboia venom at 37°C attenuates its necrotic action on animal tissues but does not interfere with its immunising power. Horses are immunised by giving them weekly subcutaneous injections of gradually increasing doses of cobra venom, heated to 70°C for an hour; this precipitates the irritant toxins without injuring the neurotoxin.

Method of preparation The technique of production of antivenenes is a complicated one owing to the now generally accepted fact that the antigenic substances contained in snake venoms are on the whole highly specific. Horses are used for the production of the antivenenes. The immunising process must be carried out very cautiously owing to the great sensitivity of this animal to the venoms. The venom from a living snake is desiccated over sulphuric acid *in vacuo* and a weighed quantity is dissolved in sterile water and injected subcutaneously into horses selected for the purpose. In the preparation of anti-daboia serum, the venom is sometimes emulsified with sterile lung tissue before injection in order to fix the hæmorrhagin principles. The M.L.D. of cobra venom for the horse is 25 mgm and therefore the first immunising dose is much smaller than this. This is gradually increased until the animal is able to tolerate 1 to 2 gm of the dried venom at a single injection. This amount is equivalent to the entire yield of 20 average-sized snakes. Usually a period of 12 to 16 months is necessary to obtain a sufficiently powerful serum. At Kasauli the final dose of venom is very much smaller and the horses are brought up to the titre in about 4 months. In order to avoid the strong reaction produced by the injection of venom into horses various substances are added by different workers to neutralize or to reduce the toxicity of the venoms. Calmette uses the solution of hypochlorite of calcium; some workers combine a little antivenene or formaline, etc. These substances reduce the toxicity but do not alter the antigenic properties of the venom. Brazilian workers prefer to use the unaltered venom in the preparation of antivenomous sera. Twelve days after the final injection the horse is bled to the extent of 8 litres, and five days later 6 litres and another 6 litres five days later, till 20 litres are obtained. In some laboratories the animal is put under chloroform and the whole blood and plasma is removed, yielding in this way 50 to 60 litres of serum; this procedure is believed to be more economical. The serum is prepared in the usual way, standardised into units on rabbits, and supplied in hermetically sealed ampoules of 10 c.cm. each. Standardisation of antivenene in Kasauli is carried out in pigeons. The minimal standards for unconcentrated antivenene are that 1 c.cm. should

neutralise not less than 1 mg. of daboia venom and 0.5 mg. of cobra venom. Higher titres are usually obtained and 1 c.cm. may neutralise 3 to 5 mg. of daboia venom. The therapeutic efficacy of the serum is estimated by titrating it before filling it into ampoules. The methods used are the prophylactic test in which the serum is given an hour before a dose of the venom, or the simultaneous test which allows the neutralisation of the serum-venom mixture to take place *in vitro* before their injection into the animal, or by the curative test used by the American authorities. Here the venom is injected intramuscularly into rabbits and twenty minutes later the antivenene is given by the subcutaneous route.

Concentration of antivenene. In snake bite, the biting snake frequently remains unidentified, and in countries where numerous poisonous species abound, resort to polyvalent antivenene has proved necessary. Polyvalent antivenenes, however, are very bulky for intravenous and intramuscular routes, and in consequence some method of increasing their potency by concentration, such as has been successfully applied in the manufacture of antivenenes in Brazil, South America and the United States, becomes highly desirable. In 1929 a polyvalent antivenene was produced at the South African Institute of Medical Research utilizing the sodium sulphate process.

Considerable experimental work has been done by Acton and Knowles (1915), Caius, Iyengar and Anderson (1924) and Mallick and Maitra (1932). Maitra, Naidu and Ahuja (1933) produced a concentrated antivenene by the sodium sulphate method. The ammonium sulphate method for concentrating sera is now in routine use.

To the plasma of immunized horses are added, (a) 3 per cent. of a 4 per cent. solution of calcium chloride, (b) two volumes of tap-water, and (c) of the total volume so obtained about 18 per cent. of ammonium sulphate. The specific gravity of the mixture is adjusted to 1099 by adding more of the salt or the tap water; it is then filtered through chain cloth folded like a concertina along the border to fit a funnel, the filtrate being returned to the filtering cloth until it comes through clear. The precipitate on the cloth represents the fibrin and the englobulin, and in the clear filtrate pass the pseudoglobulin and the albumin. The precipitate is rejected.

To the filtrate, after measurement, is added about 10 per cent. more of the ammonium sulphate and the specific gravity adjusted to 1133. The mixture is stirred, allowed to stand for half an hour, stirred again and filtered through another piece of chain cloth. The precipitate collected on the cloth represents the pseudoglobulin; in the filtrate which is rejected passes out the albumin.

The precipitate is scraped towards the middle of the cloth with an ivory spatula, the cloth being then folded in such a way over the precipitate as to leave no folds and dead spaces. It is then subjected to pressure in a hand press, the pressure being applied at first gradually

then increased quickly until dripping ceases. The hard-pressed precipitate is removed from the cloth as a cake.

The cake is weighed, broken up and put in bags of cellophane (No. 300), in quantities of about 100 gm. for each. The bags are suspended from a rod and allowed to dip in running cold water. In 12 hours the contents of the bags are found to be liquid, clear and increased in bulk. The bags are now gently squashed and allowed to sink further, to increase the surface for dialysis. In 24 hours the contents begin to turn turbid and the turbidity increases steadily and is at a maximum in 96 hours. By this time the ammonium sulphate is all dialysed out. The dialysate is collected into a bottle to which are added washings from the bags to bring the total quantity upto a convenient figure. The original volume of the plasma divided by the volume of the total dialysate gives the degree of concentration.

To the dialysate is now added 1 per cent. of sodium chloride which at once turns the turbid and viscid fluid into a clear, less viscid and translucent product of slightly greenish hue. The pH is generally found to be between 6.9 and 7.1 and is adjusted to 7.5 or 7.6 with sodium carbonate. A preservative, 0.7 per cent. of a mixture of equal parts of ether and tri-kresol, is next added and the bottle left undisturbed for two weeks. A whitish sediment, consisting mostly of euglobulin and fibres from the chain cloth, collects and clears the product further.

A sample is now tested for potency and toxicity. If the titre of protection is satisfactory and the product is not toxic it is passed through a Seitz filter and bottled. The unconcentrated serum prepared against cobra and Russell's viper venom protects pigeons against 25 to 100 M.L.D., while 0.25 c.cm. of the concentrated serum neutralises 1 mg. daboia venom and 0.5 mgm. of cobra venom. It is issued in doses of 10 c.cm. which replace the former dose of 40 c.cm. of unconcentrated serum.

The antivenomous principle can be concentrated up to 7½ times its original potency by using the methods of Pick and Boer, so that 1 c.cm. of this concentrated serum injected intraperitoneally can neutralise 1.2 mgm. of the venom as against the original serum where 1 c.cm. neutralised 0.16 mgm. intraperitoneally. According to some authorities a concentration upto 10 times is possible, but such concentrations will be of the consistency of gum and therefore unsuitable for administration. In actual practice four times the concentration is usually obtained.

The dosage and mode of administration. From the venom injected by different poisonous snakes, Calmette estimated that about 400 c.cm. of anti-cobra serum would be required to neutralise the amount of venom ejected by a cobra at a single bite or of the *Enhydryna*, which is one of the most deadly of the sea snakes. In the case of the common krait and the king cobra 600

to 800 c.cm. are required and then only if the sera are injected intravenously but Acton and Knowles considered it doubtful if a man can stand a dose of 400 c.cm. of antivenene intravenously. They estimated that in a man dying of cobra bite within two hours or less after the bite, over 700 c.cm. of the antivenene would be required to neutralise the venom, while 50 to 100 c.cm. may suffice to save patients who would take 2 to 6 hours to die after the bite. In view of the uncertainty regarding the dose of venoms which has been received, it is wiser to inject 100 c.cm. of the serum intravenously at once in all colubrine poisoning cases whenever possible. The subcutaneous and intramuscular injections of antivenene, except at the site of bite are of little value because its larger molecular weight makes absorption much slower than that of the venom. Fresh antivenene should be injected as early as possible, at least within 3 hours after the bite. With sera concentrated four times, a dose of 50 to 150 c.cm. should save every case. A rough guide for the dose is 1.25 to 2 c.cm. of the serum for each mgm. of the dried venom injected. The ratio of the neutralising power of antivenene injected by subcutaneous, intraperitoneal and intravenous methods is as 1 : 2 : 4, i.e., when tested in living animals, 1 c.cm. of the serum neutralised 0.1 mgm. of cobra venom when given subcutaneously, 0.2 mgm. is given intraperitoneally, and 0.4 mgm. when given intravenously. Russell's viper antivenene when given by these routes neutralises 0.3, 0.8 and 0.8 mgm. of the venom respectively.

The dose of antivenene to be given also depends on the rapidity of the onset of symptoms, age, site, and general condition of the bitten area, interval since the bite, season of the year and the size of the snake. The age and weight of the victim are important factors in determining the dosage; children require two or three times more than an adult because of their small volume of blood, which by itself contains a certain amount of neutralising power. Moreover the toxicity of the venom is universally proportional to the body weight of the patient. Antivenene in case of cobra bite is effective within two-third of

the death interval but Hutchison believes that it is never too late to give antivenene and that there is a chance of recovery however desperate the state of the patient may be.

There is no danger of over-dosage, rather the danger lies in not giving an adequate dose to neutralise the venom. A curative dose shows its effect almost at once or within a few hours of administration; pain is relieved rapidly and other symptoms completely disappear in 12 hours. The swelling is reduced within 24 hours. In the case of *Lachesis* the multiple hæmorrhages stop in 6 to 12 hours after the specific treatment. The patient should be kept in bed and allowed no exertion for at least 10 to 12 days after recovery. The most difficult of all are cases of Krait poisoning. Here the venom is 16 times as toxic as the cobra venom and antivenene is more or less useless. Fortunately, such cases are rare in occurrence in India.

Precautions in the use of antivenene. In desperate cases where time is of utmost importance, the possible risk of anaphylactic shock should be disregarded, and injection of antivenene by intravenous and intramuscular routes be given immediately without delay. If after this poisoning symptoms persist give another dose of 100 c cm intravenously, and a third dose later on if indicated; 400 c cm. of antivenene can thus be given safely to an average sized adult. In the case of concentrated sera 100 to 150 c cm. will be sufficient. Sometimes it happens that there is a flocculent deposit in the phials, which should be quickly filtered through a clean and sterile piece of linen before being filled into a syringe. Injections should be stopped for a short time if any untoward symptoms such as redness of the face, palpitation, reeling and embarrassed respiration appear. Keep 0.1 to 0.5 c.cm. of adrenalin hydrochloride (1 in 1,000) in readiness to be injected intramuscularly if anaphylactic symptoms occur.

Treatment of symptoms. Symptoms of shock usually develop in viperine poisoning due to destruction of the blood cells, vascular lining of the blood vessels, persistent hæmorrhage, destruction of the liver and the kidney cells, vasomotor depression, general sepsis, infection, œdema and septicæmia. Our

experimental work has shown that in such cases a dose of adrenalin chloride is the best drug and 1 c.cm. of (1 : 1,000) solution should be injected intramuscularly and repeated in an hour if necessary. Pituitrin is also useful. Blood transfusion, calcium injected intravenously, hæmoplastin, normal horse serum and adrenalin are indicated. A cup of hot black coffee is the best and the safest beverage. Aromatic spirit of ammonia may be necessary to revive the patient. Small doses of alcohol and strychnine may be given as stimulants, but the practice of giving enormous quantities of alcohol cannot be too strongly deprecated. Camphor in ether, and pituitrin may be given hypodermically as general and vascular stimulants. Rogers has advocated on physiological grounds the employment of adrenalin in viperine poisoning. In case of snake bites in which the toxins have a marked paralytic action upon the vasomotor centre, 1/16 gr. of strychnine intramuscularly has been advised to stimulate the spinal centres. Cocaine and morphine have been used locally and hypodermically to relieve pain. Sparteine 1/6 gr., digitalin 1/60 gr., pilocarpine 1/3 to 1/5 gr. and lobeline 1/6 to 1 gr. have all been tried to steady the pulse and stimulate the respiratory centre, but with no encouraging results. Five to ten c.cm. of calcium chloride (5 per cent. solution) have been given intravenously to increase the coagulation of the blood and to help the healing processes.

The fall of blood pressure and the rapid loss of blood due to hæmorrhages and extravasation lead to paralysis of the vasomotor centre. Effort should therefore be made to replace the blood by transfusion. Whole blood has been successfully injected into the peritoneal cavity or deeply into the gluteal muscles without typing or matching the blood. Intravenous injections of large doses of normal saline with 5 to 10 per cent. of glucose have given encouraging results. The dose is controlled by observing its effect on the blood pressure and pulse rate and repeated as frequently as necessary. Six hundred to eight hundred c.cm. of glucose saline can be safely injected, and a few drops of pituitrin or adrenalin may be added to keep the blood vessels in tone. Artificial respiration is of value in colubrine

poisoning as complete respiratory paralysis has not yet supervened.

RESUME OF THE ROUTINE TREATMENT OF SNAKE BITE

A. *The first aid or immediate treatment.* (1) The first aid treatment is used if the patient is seen within ten minutes of the bite. Secure absolute recumbancy. Fix a tight band immediately on the limb a few inches proximal to the bitten area and another ligature about 6 inches above. The ligature should be tight enough, but should not obliterate the arterial circulation. The part of limb having a single bone is the best site for ligature.

(2) If the bitten area is a finger or a toe apply a ligature above and amputate the bitten part within 10 to 15 minutes.

(3) If the bitten area is a flat surface or is very vascular, immediately incise it about $\frac{1}{8}$ to $\frac{1}{4}$ inch deep and $\frac{1}{2}$ inch long and forcibly express the blood and fluids as much as possible and apply suction cups or breast pump. Rub in crystals of potassium permanganate or swab well the incised parts with strong solutions of this salt.

(4) Cauterize the bitten area with strong acids, alkalies or burn it with live coal and keep the patient at perfect rest.

(5) Give stimulants like spirit of sal volatile (spt. ammon. aromat.) 10 to 15 drops in an ounce of water, coffee, etc. Keep the patient in bed.

(6) Reassure the patient that the danger of the snake bite is usually overrated and that 2/3rd of all the bites are usually from non-poisonous snakes and therefore there are more chances of recovery and less of serious consequences.

B. *Specific treatment.* (1) By the time the physician arrives there has usually been much delay, and hesitation, and indigenous remedies have been applied. His responsibility, therefore, is very great; life is in imminent danger and death may follow rapidly, he has therefore to decide quickly and act quickly. If the patient is seen early and if the bite was from a viper, he should examine the parts, tighten the ligature and excise the area.

(2) Infiltrate the bitten area with 5 to 10 c.cm. or more of the antivenene or if not available, 5 to 10 c.cm. of a 5 per cent.

solution of gold chloride or 1 to 5 per cent. solution of potassium permanganate with a syringe till the solution begins to ooze out from the wound.

(3) Inject specific antivenene as soon as possible after the bite. In cases of cobra or daboia bites, inject 80 to 100 c.cm. of antivenene intravenously within 20 to 30 minutes and give still larger doses if venom intoxication is coming on. With sera concentrated four times a dose of 50 to 150 c.cm. should save every case if given within $\frac{1}{2}$ to 1 hour of the bite. If intravenous administration is difficult, it may be given hypodermically into the sides of the abdominal wall.

(4) Inject antistreptococcal polyvalent serum as dental and oral sepsis is common in snakes. Inject intravenously 30 c.cm. of a 2 per cent. solution of calcium chloride thrice daily ; give a saline purge and ensure perfect rest.

SNAKE VENOMS IN THERAPY

Snakes and their venoms have been regarded as of great medicinal value in India. Snake venom is called *Sarpa visha* in Hindi and *Garala* in Sanskrit. The use of snake venom in Hindu medicine is of comparatively recent origin, as references to it are only met with in such modern works as *Ratnavali*, *Sarkaumudi*, etc. The Hindu practitioners obtain the poison by making the reptile bite a piece of wood, and the poison flowing out is collected on a plantain leaf. It is preserved by drying or by rubbing with a little mustard oil and spreading it on the leaf. Although the venoms of other snakes are mentioned, it is chiefly the venom of the Indian cobra which is used.

Almost all the parts of the body of a snake have been used in one or other incurable disease. Dutta (1932) has given a large list of animal products which have been used in the Hindu medicine, e.g., extracts of frogs, minced meat of lizards, skull bones of man, meat of sparrows, fat of bear and lion, feathers of the peacock, etc., have been used in different diseases. The use of cobra venom has also been advocated in the treatment of leprosy, incurable ulcers, bleeding, etc.

Ainslie (1826) wrote that the flesh as well as the skin of certain snakes were believed to possess medicinal properties in some Eastern countries. In *Ulfex Udwtieah* the flesh of snakes is described

as possessing 'hot' and 'dry' effects. The dried and powdered flesh of Jamool (an inoffensive hill snake), and the Malay Paumbou, has been advocated as a remedy against leprosy. The moult of snakes powdered and mixed with oil of *Dalbergia arborea*, when applied externally is said to be of value in epilepsy. The blood has also been used in Mahommedan medicine in the treatment of leucoderma. A preparation of arsenic and dead cobra is applied externally to leucoderma patches and syphilitic rashes in northern India. Wild tribes of North Burma and the Shan States eat the flesh of certain snakes. The venom has also been used in India as a drug of addiction, in the form of a pill. It is mixed with arsenic, opium and musk and is used as a tonic, aphrodisiac and as a prophylactic against many diseases. It has been used as a hepatic stimulant in ascites, cholera, collapse, etc.

Snake venom, particularly the venoms of *Naja naja* and *Lachesis trigonoccephalus* have been used in homœopathic medicine for the last 50 years. The venom next in importance is that of *Crotalus horridus*. Muire in South America used the venom of *Crotalus casavella*. Other venoms used are those of *Bothrops lanceolatus*, *Elaps*, *Apis mellifica* and *hachmids*. The majority of diseases in which the venom of *Lachesis* is indicated in this system are abscesses, carbuncles, erysipelas, cancer, apoplexy, paralysis, meningitis, mental diseases, asthma, tuberculosis, syphilis, chorea, flushes, metrorrhagia, hæmophilia, hæmoptysis, skin diseases, and the diseases of the teeth. Cobra venom is indicated in diphtheria and malignant tumours.

In Western medicine Rattlesnake venom (Crotaline) has been used in a number of diseases. It is said to have been employed beneficially in the treatment of pulmonary tuberculosis, acute pneumonia, pulmonary gangrene, asthma, chronic spasmodic cough, hoarseness, neuralgia, chorea, epilepsy, hystero-epilepsy and hæmophilia. The use of the venom for respiratory and nervous affections has been discredited, but quite recently interest regarding its efficacy in epilepsy has been revived. Its use in therapeutics is based on its depressing properties on the nerve cells.

It is said that the pathological effects of any given venom on man vary with the dose injected. While large doses are lethal, small doses produce beneficial physiological effects.

The rationale of application of venom in therapy. The application of venom in medicine may be based on the presence of the following active principles: (a) neurotoxin, (b) cytolyisin and absorption of granulation tissues, (c) coagulative and hæmorrhagic enzymes, production of protein and histamine-like shock, and (c) protective properties against rabies and epilepsy.

Neurotoxin. The neurotoxin principle is present in all snake venoms though it preponderates more in cobra venom as compared to

the venom of vipers and other snakes. This principle has a strong depressant action on the higher centres. Its action is particularly marked on the vasomotor and the respiratory centres. In small doses it has an irritant action, but in large doses or on prolonged contact it produces paralysis of both the sensory and motor end-plates. The venom, therefore, in graduated doses may be used to depress the higher psychical centres and is useful in delirium, hallucination, aphasia, melancholia, etc. Improvement may occur in apoplexy, meningitis, hysteria and chorea. It may be used to depress the respiratory spasms of the asthmatic attack. In small doses it may be useful in early stages of hemiplegia and paraplegia. On account of its producing anaesthesia by paralysing the sensory nerve endings it has been used locally to stop the severe pains of inoperable carcinoma.

Cytolysin and tissue absorption. The venom produces necrosis by damaging the intima layer of the blood vessels when it is injected intravenously. Recently, it has been experimentally shown that, if in the thigh muscles of a rat an aseptic space be formed by an operation and then different substances are placed in it for a period of 5 to 10 days and then the section of the wound is taken and examined histologically new inflammatory cells are seen to collect around the foreign irritant substances to form granulation tissue. This tissue reaction occurs to protect the wound against the penetration of pyogenic organisms into the tissues. In the case of cobra venom no such protective granulation tissue was formed. On the other hand the tissue cells around the cobra venom were absorbed. This shows that cobra venom has the property of absorbing the granulation tissues and neoplastic protective cells formed in the tissues. This property has been utilised in the treatment of malignant growths with the idea of absorbing the neoplastic cells of the tumour. Laignel-Lavastine and Korossios (1933) have shown that in this way the growth of the neoplasm is retarded and even the distant metastases may disappear. It cannot be claimed however that a definite cure can thus be brought about.

Hæmorrhagin, thrombase and agglutinins. Cobra venom when injected intravenously produces intravascular clotting while the viper venom and crotalin venom produce excessive hæmorrhages. Fitzsimons (1929-30) stresses that the pathologic effects of any venom in man vary with the dose injected, while a large dose may be lethal a small dose may produce only a beneficial physiological result, the doctrine of *similia similibus curantur*. Small doses of ophidian venom have been used to cure the symptoms produced by the venom itself. The hæmorrhagic and neurotoxin principles in it have been used in the treatment of epilepsy, blackwater fever and hæmophilia, etc. 'Venene' a mixture of different venoms, has been used in the treatment of menorrhagia, metrorrhagia, bleeding piles, epistaxis, purpura, hæmophilia and flushes in females.

Protein and histamine desensitization. The author (1933-34) pointed out that viper venom produces a fall of blood pressure and symptoms of shock due to paralysis of the capillaries. The shock produced appears to be similar to that of histamine or protein. The venom in graduated doses may be also used to desensitize persons against protein sensitivity. This has been done in asthma, or as non-specific protein therapy against erysipelas, carbuncles, epilepsy, etc., and it acts by producing a protein shock or suppressing allergic symptoms. Frank Coke (1934) observed that persons bitten by honey bees were cured of the rheumatic complaints. Cases have also been recorded where persons after a single bite have ceased to get attacks of epilepsy for years. Similarly the bee venom has been used against rabies since both the bee venom and rabies virus have been shown to be allied in action.

USES OF SNAKE VENOMS IN CERTAIN DISEASES

Carcinoma. Cobra venom is said to afford a means of diagnosis of the presence of carcinoma. The test depends upon the activation by cobra venom of the hæmolytic action of the serum in the complement deviation test and it is asserted that the positive test is given only by the serum of persons suffering from malignant disease. The test is known as *Farmachidi's test*.

Cobra venom has also been used in the treatment of carcinoma. It is alleged that cobra venom has the property of destroying all the neoplastic cells and granulation tissues. In rats with spontaneously grafted adeno-carcinoma injections of cobra venom produced disintegration in a few days (Calmette and others 1933). Gosset reported on the experiments done at Hospital Sâl Petrière (Paris) for the Academy of Medicine on 115 cases of every stage of carcinoma injected with cobra venom; Laignel-Lavastine and Korossios experimented on the algias of cancer patients. They found that injection of 0.001 mgm. of cobra venom relieved the pains in inoperable neoplasms in patients who otherwise had to use morphine injections daily. The injections needed repetition every 8th or 10th day.

Very small doses of venom which provoke neither suppuration nor general reaction, lead to relief of pain and cicatrization and produce other signs of healing. Epithelioma of the rectum has also been treated in this way. The distant metastases are said to have disappeared. Whatever else may have happened

the cobra venom is emphatically declared to be a good analgesic and promises a hopeful future in the symptomatic treatment of cancer.

Epilepsy and hysteria. It has been observed that in persons bitten by snakes epileptic attacks may cease for years. Spangler of the Philippines claimed that epilepsy can be cured by injections of snake venom. He used rattlesnake venom (Crotalin) till 1927 as a non-specific desensitizer in epilepsy, controlling the dosage by the degree of eosinophilia produced. A snake serum called contratoxin was also used in Texas. Claims were made by Mehnarto that by combining one type of reptilian plasma which produced hemolysis with another type which produced agglutination he could obtain a serum which produced lytic action on various micro-organisms. This serum was used in London just before the war with some apparent benefit in cases of tuberculosis, owing probably to its non-specific action in producing protein shock. Fitzsimons (1931) prepared 'venene' by blending of venoms of different species of snakes, which is said to make septic contamination impossible. This preparation has been widely used in South Africa. It is believed that alternate hypodermic and intramuscular injections of venene into the arm muscles are useful in hysteria and other nervous conditions such as neurasthenia, illusions, nervous exhaustion, asthenia, profuse and painful menstruation, chorea and paralysis. It has a lasting tonic effect on the cardiac muscles. It is said to accelerate the metabolism, soften the walls of the blood vessels and restore the circulation and nutritional processes to normal. It is believed to arrest premature senile decay. The venene treatment, however, still requires further investigation to establish its claims in therapy.

Mackenzie Wallis, W. D. Nichol, N. Craig and others have suggested the presence of an allergic element in a certain proportion of cases of epilepsy and the benefit of such as has resulted from venom treatment may well have been due to desensitization produced by its injections. In the treatment of epilepsy the venom is given in doses of 1/200 gr. by hypodermic injection, 3 to 5 injections being given at 8 days' intervals; after-

wards two more doses of 1/75 gr. are given at 14 days' intervals. If the symptoms do not disappear, another dose of 1/25 gr. is recommended. It has been advised that during treatment the administration of bromides should be discontinued. The dose and the interval of administration are to be varied according to the age of the patient and the nature of the injury. Fitzsimons pointed out that this method of treatment is not free from danger unless the venom is properly prepared by skilled hands

Asthma. Spangler (1925) used intramuscular injections of the proteins of the venom of the rattlesnake (crotalin), which contains a peptone and a globulin, for non-specific desensitization therapy in allergic asthma. An increase in the percentage of eosinophil cells, lengthening of the clotting time of the blood, increasing the permeability of the vessel walls and production of general cell and glandular stimulation are all recognised factors in the mechanism of non-specific protein reaction. He took the degree of eosinophilia produced, as a guide to dosage and frequency of administration of the proteins. Usually the highest rise in the percentage of eosinophiles following venom protein injection in doses of 1/400 to 1/50 gr. occurs by the second or third day. Within 5 to 7 days after injection, the eosinophiles will usually have dropped to 4 per cent. or less, and then the patient may be given another injection. The strength of the dose is not increased if a given strength produces an increase of 8 to 10 per cent. of eosinophiles by the second or third day after an injection. By continuing the injections the rise of eosinophiles gradually becomes less and finally does not exceed the normal limits. The patient is then non-specifically desensitized.

Uterine hæmorrhages. Peck and Goldberger (1933) treated patients suffering from functional bleeding. The venom of *Ancistrodon piscivorus* in solution of 1 in 3,000 in normal saline was used and 1 in 10,000 mertheolate was added. It is given intradermally in doses of 0.2 c.cm. and subsequent doses of 0.4 c.cm. bi-weekly; improvement occurred within 5 days to 2 to 3 weeks. In some cases six injections were given during a period of 2 to 3 weeks with the control of bleeding

anæmia also considerably improved. The treatment should be continued at least for 3 months even after the clinical improvement has manifested itself. During the first 5 to 6 injections care should be taken that the sites of injections are separated by at least 10 c.cm. ; the left arm and right thigh can be used alternately. If hypersensitivity occurs it is better to reduce the concentration of the solution to 1 in 10,000 and to continue the dose until 0.4 c.cm. of 1 in 3,000 is reached. The plan of injections to be followed is given below :—

1st injection	0.1 c.cm. of 1 in 10,000
2nd	„	0.4 c.cm. of 1 in 10,000
3rd	„	0.2 c.cm. of 1 in 6,000
4th	„	0.3 c.cm. of 1 in 6,000
5th	„	0.1 c.cm. of 1 in 3,000
6th	„	0.4 c.cm. of 1 in 3,000

Antivenene also has been used by Stockton and Franklin (1931) in case of hæmorrhagic diseases. In severe cases of bleeding, where almost every kind of treatment has failed, the patient was desensitized by giving small intracutaneous injections of antivenene in doses of 0.1 to 0.2 c.cm. every half hour and when desensitization to anaphylaxis has occurred 10 c.cm. of antivenene were injected subcutaneously on the inner surface of the thigh. The bleeding is said to have stopped almost immediately.

Hæmophilia. The coagulant action of different venoms has been suggested by various workers and has been experimented on with normal human blood and citrated plasma both *in vivo* and *in vitro*. The application of this coagulant property present in snake venoms and its use in hæmophilia was suggested by Hartridge. It has been noticed that neither coagulant nor anticoagulant action is common to any large zoological group of snakes. In allied genera the venoms of some quite nearly-related species are markedly opposite in action. The only large genus in which the venom is consistently coagulant is that of vipers. The Indian daboia venom (*Vipera russellii*) was found to be by far the most powerful coagulant agent against hæmorrhages. In the case of hæmophilia it was noticed that once the coagulation started with this venom the process

of fibrin formation was completed rapidly. The clot produced was tough and elastic, in marked contradistinction to the soft slowly forming ineffective clot characteristic of hæmorrhagic diathesis. Experimentally one drop of the Russell's viper venom in concentration of 1 in 1,000 when added to 10 drops of hæmophilic blood clotted in 17 seconds, whereas the blood from the same patient clotted spontaneously in 35 minutes. In dilutions of 1 in 100,000 the coagulation time was sufficiently short, i.e., about 60 seconds and its effect was not lost even in dilutions of 1 in 10^{18} , i.e., one in million million^{7,111,111} dilution.

These dilutions or sub-minimum lethal doses, as reported by Macfarlane (1934) produced no local effects in the form of œdema, hæmorrhages, ulceration or destruction of tissues in rabbits, guinea pigs and mice when injected subcutaneously. When applied locally to the wounds in sterile solution, they did not lead to supuration.

The coagulating property rapidly deteriorates when the venom is stored in solutions even at 0°C. or when it comes in contact with carbon dioxide. The solution is best sterilised by passing it through a Berkfield filter which does not influence its activity. Use of venom as an hæmostatic agent is indicated in, (1) dental extractions, tonsillectomy and capillary oozing in abdominal operations and (2) in hæmophilia to control epistaxis and hæmorrhages from wounds. In all cases local application of 1 in 10,000 solution was without any ill effects.

Enough data are not yet available to substantiate the therapeutic claims but the clinical trials in the above diseases have been quite encouraging.

Rheumatism. Persons suffering from chronic rheumatism are said to derive great benefit after being stung by bees. Forster prepared an ointment containing bee venom for local application in this condition. Salicylic ointment is at first applied to the skin to render it more absorbent and then the ointment containing the bee venom is used. This writer treated cases of acute and chronic articular rheumatism, sciatica and neuralgia by such applications with good results. The ointment is to be applied for 8 days, the dose of the venom being gradually increased; the treatment is then stopped for 4

days and can be continued for a longer period if necessary. The action of bees' venom is increased by producing local hyperæmia. Nowotony (1933) reports that an injectable preparation of the venom under the name of *Immenin* has been prepared and has been found very useful in chronic inflammatory processes.

OTHER VENOMOUS ANIMALS

There is a large class of other lower animals which possess glands and stings and secrete toxic chemical substances which are injurious to man and higher animals. The poisonous substances are either defensive or protective measures and play an important rôle in the metabolism and growth of the individual. Even in the vegetable kingdom these defensive and protective measures are in existence.

The animal kingdom as a whole is directly or indirectly parasitic upon the plant kingdom and, therefore, plants often fall victim to the ravages of various classes of animals, particularly the herbivorous animals which live exclusively on a vegetable diet. The defence in plants is manifest in the form of thorns, spines, prickles and bristles. These are sharp-pointed structures especially developed to ward off the herbivorous animals (e.g., in the acacia and thistle). Thorns are modifications of branches which originate from the deeper tissues of the plant. They are straight and hard and pierce the body. Some plants secrete poisonous and irritant substances in form of latex, others have stinging hairs over the leaves and stems. These hairs are tipped by glands which secrete a kind of poison. When they pierce the body the hairs break at the tip just below the gland which remains in the tissues and begins to secrete the poison and causes irritation and inflammation. Other protective measures are repulsive smell, bitter taste, mimicry, etc. which are found extensively in plants.

Among the lower animals, besides snakes, scorpions, centipedes, sea anemones, insects, bees, hornets, etc., often poison man and they are described here.

1. Sea anemones. These include sea anemones, jelly fishes (*Rhizotoma pulini* and *R. cuvieri*) of European and Mediterranean waters. All these varieties possess certain specialised cells called *cnidoblasts*, i.e., little sacs which contain a spirally-coiled filament surrounded by poisonous fluid. When stimulated these cysts explode, the filament is ejected and pierces the skin and in this way introduces the poison. These sharp and fine filaments have been called stings.

Symptoms. The stings from anemones cause itching and an intense burning sensation which are the first symptoms ; rashes and even skin eruptions follow later. A papule appears at the site of contact, followed by a red, blue and then a black coloration. This may slough or an ulcer may form.

The exact nature of the chemical substance of the venom is not yet clearly worked out. Two poisonous principles named *thalassin* and *congestin* have been isolated. The latter is very toxic, whilst the former is less toxic and only locally irritant. The jelly fishes of the tropics also produce severe local reaction, e.g., redness, swelling and urticarial eruptions may occur.

The treatment consists in application of alkalies such as diluted ammonia to the affected area and giving analgesic drugs to relieve the local agonising pain. Collapse if present should be combated in the usual way.

2. Helminths. Next in zoological order come the intestinal worms, as *Dibothriocephalus latus* and *Tænia saginata*, *Ankylostoma duodenale*, *Ascaris lumbricoides* and *Tænia echinococcus*. All these secrete a form of poison which is absorbed from the gut of man and produces profound anæmia and cardiac symptoms. The treatment consists in getting rid of the helminths from the body.

3. Toads. The venom of *Bufo marinus* in whatever way it is introduced produces the same toxic effects. There is an initial phase of excitation followed by convulsions and then depression, paralysis and gradual failure of the heart and respiration. If introduced locally it produces a localised œdema and foetid gangrene. In the mucous membrane of the eyes and the nose, it produces ischæmia and anæsthesia followed by dolorous congestion and hypersecretion and even leads to panophthalmitis. The venom has a cumulative effect. If death has been quick the post-mortem examinations show visceral hæmorrhages, cardiac infarcts and pulmonary œdema.

4. Arthropoda. This class consist of scorpions, spiders, centipedes, etc.

(a) **Scorpions** These belong to the class of *Arachnida* characterised by a stout tail armed at the end with a sting. They vary a good deal in size and in their poisonous properties. The large scorpions met with in India belong to the genera *Buthus* or *Palamnæus*. The poisons of different kinds of scorpions differ quantitatively and qualitatively. The method of striking is to bring the tail which consists of the last 5 segments forward over the body so that the curved spine in its last segment of the tail penetrates into the skin of the victim. Two poison glands are situated in the last segment, and open through a duct on either side of the curved spine which is used in stinging.

The body of the scorpion is divided into a cephalothorax (*prosoma*), the broader portion of the abdomen (*mesosoma*), next followed by smaller

five segments (*metasoma*) popularly called a tail. The terminal post-anal segment (*telson*) is armed with a barb or a sting. The appendages consist of a three-jointed 'chelicerae' which are used for holding the prey, a pair of large six-jointed 'pedipalpi' for seizing the prey and four pairs of seven-jointed legs. The scorpion holds the prey with two pairs of forelimbs brings it near its mouth and if necessary stings it by inserting the tip of the telson into the animal. The scorpion's venom is a thick, oily, clear or faintly yellow coloured fluid having a specific gravity of 1.092. It is faintly acid in reaction and contains no cellular elements. It contains 28 per cent. of solid matter and on drying forms crystals. The maximum amount of venom in the glands of *Buthus tumulus* is 5.2 mgm.

It is believed by various workers that the active principle is in the form of a nucleo-protein, acid albumin or a primary protease. The poisonous action resembles that of the neurotoxin of snake venom and the hæmolytic principle is like that of viper venom. Calmette has shown that the venom of *B. occitanus* can be neutralised by cobra venom. Lecithin and cholesterin are also present in the scorpion venom, and it can be digested by pepsin and trypsin and can be oxidised by permanganate of potash and calcium hypochlorite.

The M. L. D. of the venom for white mice of average size is 0.05 mgm. and for rabbits 0.5 mgm. The dog, the rabbit and the guinea-pig are more sensitive than the mouse or birds. The frog is more resistant than mammals. The palamænus venom is far less toxic than *buthus* venom.

The venom in the scorpion is not only a means of defence, but is also used to kill its prey. The venom is only toxic when injected subcutaneously or intravenously and has no ill effects if taken by the mouth. The scorpion venom is said to resemble closely the snake venom in action. The venom paralyses the nervous system and death in animals is due to the curare-like action on the nerve end-plates especially of the muscles of the respiratory system. It produces coagulation of blood, hæmorrhages due to injury of the capillary walls and leads to formation of emboli due to agglutination of the red blood corpuscles. It increases the lachrymal, nasal, salivary, laryngeal and tracheal secretions due to its action on the vagal and spinal centres. On the intestines it acts like pilocarpine and by increasing peristalsis it produces vomiting and purging. The venom is rarely fatal in man and is not any more dangerous than the bee or wasp venom.

In man the symptoms of the bite are redness, swelling, intense burning pain radiating from the site. This is followed by weak pulse, quick and hurried respiration, convulsions, mental disturbances, hallucinations, marked salivation and lachrymation, and profuse sweating and polyuria; abortion may occur in pregnant women. The nervous system becomes highly irritable, reflexes are increased,

tremors, muscular twitchings and spasmodic movements later followed by paresis or paralysis of the individual muscles may occur. There may be a locomotor paralysis, nystagmus and blindness. The sting is rarely fatal in adults, but it is not infrequently fatal to children. The sting of *B. quinquestriatus* is fatal in 60 per cent. of children under five years of age.

TREATMENT. The principles that guide the treatment of snake bite apply in general to that of scorpion sting. A proximal ligature, incision of the wound and sucking out of the venom and application of potassium permanganate are useful as in the case of snake bite. If possible immediate injection of immune horse serum will be very efficacious. Washing and bathing of the part with weak solution of ammonia or borax, and local injection of colloidal manganese may be tried. Five to ten min. of a 5 per cent. solution of cocaine subcutaneously in adults and 1 to 5 min. in children around the site of the wound help in relieving the pain. Eucain and stovaine may be conveniently substituted. Tyrosin and juice of dahlia are said to have a neutralising action on the venom. Buchmann considers local injections of 1 per cent. solution of tucocain in 2 cm. doses, given subcutaneously, to be a good remedy.

Antiscorpion serum. Metchnikoff (1901) observed that the blood of the scorpion is distinctly antitoxic against the scorpion venom. Todd (1909) prepared an antiserum from the Egyptian scorpion and showed that it acted both prophylactically and curatively in animals and in man. Employed curatively it relieved the intense pain of scorpion bite. Antivenene against scorpion sting is prepared at the Butantan Institute in Brazil, in the Pasteur Institute in Algiers, the Lister Institute, Elstree, England and the Behring Institute in Germany. The scorpion serum is not prepared in India for there appears to be no necessity for it. The antivenene prepared at Kasauli (India) against cobra and daboia venom imparts a certain amount of protection in rabbits and dogs which have received a lethal dose of the venom of *B. tumulus* and *Palamnaeus swammerdami*. None of the Indian plants recommended for the treatment of scorpion sting in indigenous medicine was found by Cains and Mhaskar to have any preventive or antidotal effect. Lately, Sergeant and Sergeant (1934) have noticed that the venom of Algerian bees (*Apis mellifica*) has some immunising power against the scorpion venom (*Butus occitanus*).

(b) **Spiders.** This group is called *Aranea*. The spiders are found all over the world, but by far the largest ones are met with in the tropics. The species having the spinning organ just in front of the anus and having no tegral plates visible are interesting from our point of view. This variety is called *Opisthothelae*. These are further divided into two tribes as *Megalomorphae* and *Arachnomorphae* depending on the site of the spinning organs. There is a great deal of misconception regarding the bites of spiders. The common spiders usually do not bite

but when they do bite the bites amount to no more than a pinprick. In California, Brazil, South Russia and Australia toxic and even lethal effects in man and animals from the bites of poisonous spiders have been recorded.

Medical text books devote very little attention to the spider bites. But the bite of the 'black widow' (*Latrodectus mactans*) is quite serious and may even prove fatal. The venom of the venomous spiders resembles that of the scorpion in appearance and action. It is a thick, oily, translucent, lemon-yellow coloured fluid, slightly acid in reaction and is bitter in taste. It dries at 37°C. forming a light yellow powder. Kobert and Sachs have found a *haemolysin* and an *arachnolysin* in the several types of spiders. The *arachnolysin* acts upon the erythrocytes in man, rabbit, ox, mouse and goose, but not on those of the horse, dog, sheep and guinea-pig; 0.5 mgm. of the venom when given intravenously causes death in guinea-pigs of 600 gm. weight in less than two hours. Bogen succeeded in immunising rabbits by the administration of graduated doses of the venom. The venom has injurious effects on the isolated heart of the frog, and the capillaries are injured; this leads to marked transudation of fluid and oedema. The venom acts on the central nervous system producing cramps and convulsions. Locally, inflammation is followed by dry necrosis of the skin. There is severe pain at the site of the bite followed by radiating pain and swelling in the whole limb; sweating, palpitation and rise of temperature are present. In the case of Corsican scorpions (*L. tridectinguttalus*) erection of the penis and anuria occur very frequently. Later, an eruption may occur which consists of a general invasion by red lenticular spots, non-confluent and not disappearing on pressure. Bronchial constriction plays an important part in determining the fatal issue.

TREATMENT. The main effort should be to prevent the absorption of the poison by application of a ligature and to open the wound and wash it with a solution of permanganate of potash, or an alkaline solution such as a weak solution of ammonia or carbonate of potassium may be used. If the bite is not of a serious type the parts may be kept covered with a dressing soaked in a solution of ammonia and water or with permanganate of potash. In the case of the bite of Bengal spiders, Fink recommends the exposure of the bitten area to the smoke evolved from lumps of mustard oil cakes, burned on a charcoal fire and dropped into a basin of cold water. De Asis Cesareo (1934) has used intravenous injection of a 25 per cent. magnesium sulphate solution with marked benefit in the case of the 'Red back' spider of the Philippines, which is sometimes fatal. This venom has a special predilection for the peripheral nerves and nerve end-organs. Other symptoms produced are elevated blood pressure, weak pulse, general weakness and numbness, muscular pain and paralysis of the lower limbs. Brazil and Vellard have prepared a bivalent antivenene by immunising sheep and have demonstrated its therapeutic efficacy in man; rapid improvement follows its use. The

spider antivenene, in common with those derived from snakes and scorpions, is highly specific.

(c) **Ticks (*Acarina*)**. These are well known to cause severe symptoms by their bites apart from the introduction of parasites such as *Piroplasma* or *Spirochæta*. The ticks pierce the skin by means of their teeth on the digits of their chelicerae. The bite causes itching or severe pain, fever, lassitude, even delirium and convulsion. Death occurs in rare cases.

The properties of the venom are comparable with those of other arachnid venoms. When introduced into the dog, rabbit, guinea-pig, rat and mouse, it produces progressive motor paralysis. It is important not to remove the tick forcibly, as the mouth parts are thus broken off and remain in the skin. If in removing the tick, the parts of the jaw remain in the skin, there is a possibility of infection which may lead to sloughing of the surrounding tissues. The first thing therefore to do is to detach the tick which is by no means easy as the curved teeth hold on the wound very firmly. The best plan is to rub any bland oil on the ventral surface of the tick. This interferes with its respiration stigmata and compels the tick to loosen its hold and it drops off in a minute or two, or it may be removed by excising a small piece of skin at the site of its attachment.

The bitten area should be bathed with very hot water, and then a concentrated solution of bicarbonate of soda may be applied. A 1 to 2 per cent. ointment of menthol may be rubbed in locally to allay the intense itching. Huts infected with ticks should be burnt down or fumigated with sulphur, carbon disulphide or sprayed with kerosene oil and hot water. The feet of beds should be placed in cups containing water and kerosene oil, and the coverings of the bed may be dusted with pyrethrum powder or camphor powder.

(d) **Centipedes (*Chilopoda*)**. Centipedes are common all over the world, but the tropical species are much larger than those found in the temperate zone. The poison apparatus is formed by the appendages of the first trunk segment, which is modified to form a large pair of jaws and at the base of this the poison gland is placed. The duct of this gland opens on the apex of the claw and there are two jaws; a centipede bite will show two minute punctures or drops of blood. As the legs have no poison glands it is difficult to account for the frequently reported cases in which the centipede in travelling over the skin has left an urticarial trail. It is possible that some of these cases have been cases of caterpillar sting.

The venom resembles scorpion venom and is primarily intended to kill the prey which consists of small insects and larvæ. It is an opalescent liquid, acid in reaction, and miscible with water. A solution injected into the rabbit's ear vein produces immediate paralysis and coagulation of blood.

The symptoms are those of itching, intense pain extending along the whole limb followed by lymphangitis and lymph adenitis. The

bitten spot becomes red and swollen and finally black. There may be great mental anxiety, vomiting, irregular pulse, dizziness and headache.

Treatment is the same as in the case of other poisonous insects. The swelling may be reduced by applying an ice bag. It may be necessary to inject morphia to relieve pain.

(c) **Bees (*Apidae*)**. Stinging from bees is not infrequent in man, and in the tropics people are often severely bitten by bees and suffer very much, though occurrence of death is rare. Bees belong to the order of *Hymenoptera* which also includes wasps, hornets and ants. Bees are very common in India particularly the hive bee (*Apis mellifica*); the wasp (*Vespa vulgaris*) and the hornet (*V. orientalis* or *V. crabo*) are also met with everywhere.

The venom of bees has been studied by Brandt and Ratzeburg (1839), Paul Bert (1865), Carlet (1884), Josef and Langer (1897) and Phisalix (1904) and others. The body of the bee is divided into head, thorax and abdomen from the posterior end of the last of which projects the sting in the form of a chitinous sheath, narrow posteriorly and wide anteriorly. There are two, sometimes three, poison glands in the abdomen which open into a sheath round about the sting. The sting consists of a central shaft and a pair of barbed darts.

The bee venom is a transparent acid fluid, bitter in taste, aromatic in smell and has a specific gravity of 1.1313. The acid reaction is due to formic acid, but it is not the active principle, and the properties of the venom, as was formerly believed, do not depend upon it. The venom resembles cobra venom in containing substances which produce local inflammation, substances which act on the nervous system and substances which produce hæmolysis. Intravenous injections of the venom into dogs and rabbits produce tremors, convulsions, nystagmus, emprosthotonos and death from respiratory failure. The action of the venom is probably both on the nervous system due to neurotoxin, and also on the blood as it produces marked hæmorrhages in the visceral organs. Injected into human skin it causes a reaction identical with that caused by diluted rattle snake venom and by histamine. A case is on record when a girl of 7 bitten by a bee developed a violent explosion of hay fever which was controlled by ephedrine. The child had otherwise no susceptibility to hay fever.

The symptoms from the bite are pain, redness and swelling of the area which disappear after a few hours. Suppuration and blood poisoning are rare complications. In weak and old people there may be constitutional symptoms such as nausea, faintness, vomiting, difficulty in breathing and eruption on the skin. In cases of multiple stings or in stings of some of the hornets there may be considerable constitutional disturbances amounting even to collapse. Later, there may be slight fever, cedema, urticaria or macular eruptions on different parts of the body. It may lead to partial loss of consciousness. There

may be cold and clammy sweating, irregular and weak hardly perceptible pulse and signs of shock. All the apidæ may cause severe symptoms if the bites are extensive and particularly on spots like the eyes, ears, and lips or in very old people and young children.

Treatment. In the case of the honey bee, the sting, with the poison glands attached, is frequently left in the wound, but in the case of other bees, wasps and hornets, the sting is not left in the wound. If the sting is left in the wound it should be removed by lifting it out with a knife so as to avoid squeezing out any more venom into the wound. Hot applications are of great value. The usual applications of alkalis, solution of ammonia, carbolic acid (1 in 20 or 1 in 10) if applied immediately on the stings, bring satisfactory results. Potassium permanganate may be tried. Calcium hypochlorite (1 in 60), ice compresses or ice bags are also useful.

Insects, wasps, beetles, etc., also give troublesome pain. The treatment in all these cases is almost the same as mentioned above.

(f) *Ants (Formicidæ).* In the tropics the bites of some of the large ants are very painful and may cause faintness, shivering and at times temporary paralysis. Ordinarily the bite of an ant amounts to no more than a sharp stinging possibly with the development of a wheal at the site of bite. The venom contains formic acid, but from the severe effects of the bites of some of the tropical species it appears that the venom must contain other toxic substances as well. The treatment consists of bathing the bitten parts with dilute solution of ammonia. Ants can be kept out of beds by placing the legs of the bed in cans filled with water with a layer of oil on the top (to prevent mosquito breeding) or by sprinkling powdered camphor between the sheets.

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CHAPTER V

DRUG ADDICTION AND ITS TREATMENT

From time immemorial mankind has tried to attain degrees of emotional intensity and duration, which are otherwise unknown to the brain. It took recourse to consuming substances of no nutritive value, solely for the purpose of exciting the function of brain centres which transmit agreeable sensations and to maintain for sometime the consciousness of experienced emotion. The habitual use of alcoholic beverages and certain vegetable substances for stimulative and restorative purposes has thus gained a strong foot-hold in the daily life of human beings all the world over. The earliest records available show that opium and certain other narcotic drugs, *e.g.*, mandragora, hyoscyamus, hemlock and others are amongst those commonly used.

Addiction to drugs is met with all over the world. The inducements which bring about the first recourse to the use of a narcotic drug are varied. Some take them out of curiosity while others from a deliberate intention to experience a pleasant though temporary change in the mental state. It has been stated that prolonged use of certain drugs taken during illness as medicines has also claimed its victim in certain cases. Such patients, overcome by their influence, become habitual drug takers. The drugs used vary in their action, some of them being stimulating, others depressing ; each of them gives to its devotees a certain measure of comfort and pleasure tending in a curious and inexplicable way to create a craving for more of the drug and in a greater or less degree gives rise to drug habit. With many there are no ill-effects, but the habitual use of opium, morphine, alcohol, cocaine, etc., leads to grave moral and physical degradation and the difficulty of breaking the habit has to be faced. Addicts are recognised as persons who, not requiring continued use of a drug for relief of symptoms of organic diseases, have acquired, as a result of repeated administrations, an overpowering desire for its continuance and in whom with-

drawal of the drug leads to definite symptoms of mental or physical distress or disorder. Addiction thus becomes a disease which necessitates proper treatment.

Influence of the climate and other factors lead to habitual use of drugs in the tropics and in countries like India the physician has often to face the problem of treating drug addicts. It was, therefore, thought necessary to introduce the subject in this work.

Drug addiction in India. The problem of drug addiction in India presents many features which are widely different from those met with in the Western countries and about which a great deal of misapprehension exists in Europe and America. The habitual use of drugs of a stimulative and restorative character was prevalent in India probably long before it was in any of the other countries of the modern world. The juice of the *Soma* plant was a favourite drink of the Aryan settlers and was regularly taken by them many centuries before the Christian era. What exactly was the *Soma* plant is not known, though a number of plants such as *Cannabis sativa*, *Ephedra vulgaris*, *Asclepias acida*, have been implicated. During the Hindu period, i.e., up to the 8th or 9th century A. D., alcoholic beverages were used by the people as well as the preparations made from hemp drugs. These produced not only a sedative effect, but also brought about euphoria in the form of pleasant dreams, forgetfulness and, it would also appear from the writings of that period, voluptuous satisfaction. Opium and poppy were introduced on the west coast about the 9th century A. D. by the advent of the Mohammedan traders, and opiates soon came into use. A study of records shows that during the period of the Moghul Empire, alcoholic beverages, opiates and hemp drugs were freely used. A decoction made from poppy capsules known as 'koknar' was extensively used all over India, and is used to the present day in parts of the Punjab. A beverage containing wine, opium, Indian hemp and poppy capsules, known as 'charbargha' (four-leaved) was drunk by the well-to-do classes in the time of Akbar (1556 to 1605) and later. Opium on account of its stronger effects appears to have taken a great hold of the people and poppy was extensively cultivated all over the country during this period and was indulged in by all classes.

Opium. *Opium eating and smoking.* Most of the raw opium sold in this country is used for addiction purposes in one form or another. It is generally consumed in the form of a pill or solution in water. Opium smoking although not common is still practised by the lower strata of the society in many parts of the country. It is common in Assam and in certain parts of the Central Provinces and Berar. The proportion of opium smokers to opium eaters in Assam has been variously estimated from one third to one half of the total addicts but our recent enquiries

show that the number has now come down to a quarter. The government of India and all the provincial governments have adopted the policy of checking opium smoking by diminishing the facilities for the practice of the habit through legislation. These measures have succeeded to a great extent and as a result of this the habit has greatly declined.

Although opium is habitually used by large sections of the population at the present time, the indulgence is not so widely prevalent as might be imagined from some of the recent publications on the subject. The Government of India have strictly adhered to their promise to the League of Nations and have progressively reduced both the production and consumption of opium. It has been shown that although if the country is taken as a whole the consumption of opium is low, in certain parts it is very high. For example, in Bengal Presidency taken as a whole, the consumption per 10,000 of population is 8 seers per annum, instead of 6 seers as required for the medical and scientific needs. In the town of Calcutta it is 58 seers, in Hooghly district 21 seers, Howrah 16 seers and 24 Perganas 15 seers. In the Madras Presidency as a whole it is 8 seers, but for East Godavari and West Godavari it is 37 and 22 seers respectively. For the Punjab as a whole it is 12 seers, but for Ferozepore district 33 seers, Lahore 34 seers, Ludhiana 25 seers, Amritsar 30 seers. In the whole of the Central Provinces and Berar it is 9.0 seers, but in Amraoti it is 40 seers, Akola 50 seers and in Balaghat 30 seers. In Assam as a whole it is 19 seers, but in Lakhimpore it is 70, Sibsagar 45, Nowgong 27, Darrang 22 and Kamrup 8.9 seers. The highest consumption recorded in India is in Sadya frontier tract, being 94 seers. The higher figures are due to smoking of the drug, which necessitates a much higher consumption per head. On the other hand, there are extensive areas in all provinces where consumption is very low, i.e., 1 to 5 seers per 10,000 of population per annum. Such areas are now on the increase. In Assam, Goalpara and Sylhet are examples of such places. In the Punjab there are 20 out of 29 districts where the consumption is below the standard laid down by the League of Nations, as being necessary for purely medical and scientific needs of the population, i.e., 6 seers or 12 pounds per 10,000 of population per annum.

It will thus be seen that the habit is not widely disseminated among the population, its incidence among various classes is very irregular and although there are admittedly certain areas and certain classes of population which are badly affected, there is evidence to show that in many parts of India the consumption of opium is below the standard laid down by the League of Nations. These areas with high consumption rate are being investigated with a view to determining the causes which have led to increased consumption and steps are being taken to put down excessive use. This is evident from the following table.

Year.	Consumption of opium in seers in British India (excluding Indian States).			
1912-13	5,06,864
1930-31	2,41,211
1931-32	2,13,000

N.B.—1 seer is approximately equal to 2 pounds.

The average dose taken in the writer's recent series of over a thousand cases was roughly 10 gr. daily per addict as compared with 20 gr. worked out by the Opium Commission of 1895. The problem of addiction to opiates in this country, although it is still very extensive, does not appear to exist in such intense and pernicious form as it does in the West with morphine and other alkaloids of opium. It may be stated here that in old days, when opium was cheap, addicts were undoubtedly found who took 180 to 500 grains of the drug daily. The writer in recent years has met with only a few individuals who took more than 50 gr. daily; many of the old addicts however take more than 15 gr. daily. The chief reason for smaller dosage is that the price of opium has risen enormously. Whereas during the pre-British period, in the Punjab, opium used to sell at 2 to 3 annas (2 or 3 pence) per 'tola' (180 gr. or 12 gm.), in 1901-02 it cost 8 annas for the same amount and in 1929-30 Re. 1-12-0 (2 shillings).

Administration of opium to infants. Habitual administration of opium to infants at certain periods of their life has been prevalent in India for many centuries. The habit appears to have been started because of the drug's power of allaying diarrhoea and vomiting, relieving cough and pain, and producing sleep. The custom, although it is still met with in almost every part of India, has greatly declined during the last two or three decades. The drug, however, is still extensively employed in the Central Provinces and Berar and in the industrial areas in all parts of India. In Berar it is stated that 75 per cent. of the infants are doped with opium and 25 per cent. of the total opium consumed goes to infants. The consumption is still higher in the cotton-growing areas where children account for 40 per cent. of the total consumption. The main reason for administering the drug is economic, the drug being given to keep the children quiet so as to allow the mother to carry out her work, whether in the factory or the field, unhampered. The practice is begun during the first few weeks of the infant's life, the earliest time to commence being 3 weeks and the latest period 3 months. The drug is usually discontinued when the child attains the age of 2 or 3 years, that is when it begins to play about and can live on ordinary food. The dose varies from one eighth to three grains daily. The drug affects the child's health adversely and hinders growth. The children receiving opium have an emaciated, unhealthy and toxsemic appearance.

They are more liable to catch infections and attacks of epidemic diseases and the mortality rate among them is comparatively high. Although deaths from overdosage are not frequent they do occur. Non-fatal overdosage is not uncommon.

Addiction to 'post' (unlanced capsules of *Papaver somniferum*). The poppy capsules are known to have been used for their soporific properties by the ancient Egyptians, Greeks and Romans. For many centuries they have been used in the Chinese, Hindu and Mohammedan medicine as sedative in inflammatory diseases of the alimentary and respiratory tracts. During the 16th, 17th and 18th centuries when the Moghuls were in power in India, the capsules were extensively used to prepare a beverage which had soothing and euphoric effects and which was almost universally indulged in. The habitual use of poppy capsules for euphoric purposes has considerably decreased during the last three decades but the addiction is still prevalent in certain districts of the Punjab, and in many parts of the Rajputana states, especially Jaipur. The present writer after a careful study of over 500 addicts has come to the conclusion that habitual use of poppy heads produces physical, mental and moral degeneration in the habitue. As compared with the opium habits its effects on the individual are much more pronounced.

Addiction to opium alkaloids. Habitual use of morphine has considerably increased in India during recent years, the increase at present being confined to Northern India. There appears to be grave danger of rapid extension of this habit to other parts if steps are not taken to check it. Morphine addiction among Indians is usually met with in young persons between the ages of 20 and 25 years. The habit is not started for the sedative and analgesic effects of the drug as in Western countries, but for its euphoric effects and because of its supposed aphrodisiac properties. Formerly the alkaloid was taken almost exclusively by the mouth, but recently the injection method is coming into use. By this latter method, the effects produced by the drug on Indians are very similar to those produced by cocaine. The habit produces a state of chronic toxæmia and detrimentally affects all tissues of the body particularly the nervous tissues. In morphine habitues the physical, mental and moral deterioration sets in much more rapidly than in opium addicts. Addiction to other alkaloids of opium, e.g., codeine, heroine, is very rarely met with in this country.

Indian hemp. It grows wild in the montane and submontane tracts over the whole of north-eastern and north-western parts of India and three of its preparations, i.e., *bhang* (dried leaves), *charas* (resinous exudate) and *ganja* (flowering tops) were largely used by the poorer classes on account of their very low cost. Even to the present day hemp drugs are the narcotics extensively employed by the poorer classes throughout the country. Extensive work in the field has enabled the writer to estimate approximately the prevalence of hemp drug addiction in India.

and taking the country as a whole the incidence of addiction in British India ranges between 0.4 to 0.8 per cent. of the population. In Southern India, where the spontaneous growth of *Cannabis sativa* does not occur, hemp was and is still cultivated for use as a drug of addiction. The physical effects produced by these drug habits are not so marked as those of opium but they undoubtedly lead to physical, mental and moral degeneration. When under the effect of these drugs, the addicts appear to lose all idea of correlation of time and space. They forget their environments and do not know what they are doing. *Ganja* and *charas* are much more potent in this respect than *bhanga* and their excessive consumption, especially of the latter, gives rise to insanity and leads to crime. This was one of the points discussed by the Hemp Drugs Commission, but no definite conclusions could be arrived at.

Alcohol. The use of distilled alcoholic liquors has extended during the early part of this century but has reduced lately. In old days distilled liquors were used to a very limited extent; wines were largely used. The aboriginal races of India made a beverage by fermenting rice—*pachwai*—and by fermenting palm juice—*tari*. Both these are extensively used in many parts of India to the present day. The main fluid that is habitually drunk by the Nagas of Assam Hills (Manipur State) is a weak country beer called *zu*. It has been shown that the alcoholic content of the majority of the crude beers used in India is low and their nutritive value is very high. Some of these beers are rich in vitamins which are often poor in the dietary of the people who drink them. The areas where such beers are consumed are remarkably free from deficiency diseases. Distilled country liquors and foreign liquors are used by the richer classes to a comparatively lesser extent. The drinking of youth and the social drinking in the endeavour to mitigate the wear and tear of life and to get relief from its annoying factors, as it exists in the West, is not commonly found among Indians. Extensive habitual use of alcohol is uncommon and the harmful effects produced by it are rarely encountered. The problem of alcoholism has not up to the present time assumed a serious aspect in this country. It may however be pointed out that the use of distilled country liquors is increasing in certain areas and in many parts of India drunkenness is being more frequently met with among the masses. This is due to the fact that while restrictions are being imposed on the sale of opium and hemp drugs their price has risen owing to increase of excise duty, but in spite of the high excise duty a bottle of distilled liquor can be purchased for a few annas. Country liquors in many parts are taking the place of opium and hemp drugs.

Cocaine. The present writer (1931) has shown that cocaine came into use quite accidentally about 50 years ago. In spite of all the restrictions imposed on the import, possession and sale of the drug, the

habit has spread from Calcutta to large towns along the two main railway routes through the Central Provinces into the Punjab and the North-West Frontier Province. From Bombay it spread to some of the large towns in that presidency. Cocaine is not manufactured in India but is smuggled into the country in large quantities. For some time past the Far East has driven the European and American manufactured product out of the market. The drug is illicitly brought by crews of ships running between Calcutta and the Far East and is heavily adulterated before it is sold. Cocaine is usually taken in the form of an injection or as a snuff in Western countries, but at present practically the only method of taking the drug in India is by the mouth. It is commonly consumed by putting it in *pan* or betel leaf and for that reason addiction to this alkaloid is prevalent among the betel-leaf chewing population of North-West India, Bengal, Bihar, the United Provinces and the Punjab. The habit not only exists among the well-to-do people but a large number of the artisan class in large towns are also addicted to it. It has been calculated by competent authorities that over 200,000 ounces of cocaine were smuggled into India in 1929 and that the consumers paid between Rs. 270 lakhs and Rs. 648 lakhs to the retailers for their doses of the drug. The symptoms and effects produced by it were studied in 200 cases (1931).

New drug habits. During the last few years chloral hydrate as a drug of addiction has also made its appearance in Northern India. It has come into use since the price of spirituous drinks has gone up considerably on account of the increased excise duty. Many of those that drink alcohol habitually in India do not take it merely to obtain mild excitement or sedative effects, as is usually the case in the West, but to obtain intoxicating effects. Owing to increase in the price of liquor they cannot afford to buy sufficient quantities for this purpose and the ingenious idea of potentiating the effects by adding small quantities of chloral hydrate (0.5 to 1.0 gm.) has occurred to them. The drug is sometimes mixed with tea and is habitually consumed by some people. Chloral habit has thus sprung up though fortunately a very limited area is affected at present. The drug is powerful and toxic and several fatalities have been reported from accidental overdoses. Chloral hydrate is a cheap product selling at about Re. 1-12-0 per pound, and as there are no restrictions to its sale at the present time it can be bought by any one in any quantity from the chemist's shop. Half to one gramme or a little more added to an alcoholic drink produces symptoms of intoxication followed by sleep. The habit is harmful and dangerous. It is much more liable to produce pathological changes in the organs and immediate fatal results than any other drug of addiction in this country. The mental, moral and physical effects produced by this addiction are more pronounced than any other drug habit. The drug is cheap and is easily procurable as there is no control over its sale and these factors are largely responsible

for the spread of its use among the population in certain localities. There is a danger in the use of chloral hydrate for adulteration of alcoholic beverages (toddy, rice-beer, etc.) being extended and of the further spread of chloral habit.

Barbituric acid derivatives. A number of fatalities resulting from indiscriminate therapeutic use and self medication with these drugs have occurred and a few cases of addiction have also been observed among the educated classes in India. The fact that besides the toxic effects produced by massive doses, the barbiturates also produce dangerous cumulative effects and a tendency to habit formation has not been sufficiently appreciated by the medical practitioners in this country. A warning is therefore necessary. The need for bringing the sale of drugs like chloral hydrate, butyl chloral, paraldehyde, sulphonal, bromural and barbituric acid derivatives under a more strict control is very urgent.

Briefly then the principal habit-forming drugs used in India are :—

I. Opium is still extensively used both by adults and infants. *Post* or *koknar* (unlanced capsules of *Papaver somniferum*) were largely used at one time, but owing to restrictions in the cultivation of the poppy, that use is now limited to a small area in Northern India. The use of morphine, though uncommon, is gradually increasing.

II. Hemp drugs. *Bhang* (dried leaves), *charas* (oleo-resinous exudation) and *ganja* (dried flowering tops coated with resin) are extensively used all over the country by the lower strata of society on account of their very low cost.

III. Alcohol. *Pachwai* (fermented rice) and *tari* (fermented palm juice) are largely used by poorer classes. Distilled country spirit and imported liquors are used by the richer classes.

IV. Cocaine was introduced fifty years ago; its use is spreading in Northern India.

V. Chloral hydrate has been introduced during the last 10 years; barbituric acid derivatives are being tried. The use of these drugs at present is limited; but there is danger of their extension for adulteration of alcoholic beverages.

Ætiological factors. It will be observed from the fore-going that the first three groups of drugs which are commonly used in India, are mostly raw and crude products. In many cases they have to be prepared by the addict himself before use, which in itself limits their excessive consumption. Further by the use of crude products the addicts absorb comparatively smaller quantities of the active principles which are responsible for producing the toxic effects. In Western countries almost all the drugs used for addiction purposes are highly purified products such as morphine, heroin and cocaine. Moreover many of these drugs in the West are taken in the form of injections. This method brings about the action more quickly and more intensely. At the same time the action is not so lasting as when the drug is taken by the mouth. All these factors lead to a greater desire or craving on the part of the

addict for more frequent repetition of the dose and the habit is liable to be carried to excess and the addict to become a danger not only to himself but to the society. In India most of the common drugs of addiction are taken by the mouth and being crude products never produce such intense effects as are observed in Western countries. A large number of addicts from the lower strata of society are so poor that they have not the means to carry the indulgence of even the crude and cheap drugs to an excess; the upper classes are temperamentally moderate. Besides India is pre-eminently an agricultural country which makes it possible for the majority of its inhabitants to lead a comparatively free and easy existence. The strain and stress of life which drive people to the habitual use of sedative drugs are not so great as in the West.

In spite of all these factors the problem of drug addiction is of very great importance from its extensiveness. The magnitude of the problem can be judged by the fact that whereas in most of the countries in Europe and America the addiction rate of the population is from 0.1 to 0.2 per cent. or even less, in many parts of India the rate is 1 to 3 per cent. or even more. These drug habits are responsible not only for much economic loss but also lead to physical and mental deterioration and are of very great importance from a health point of view.

Another noteworthy feature of drug addiction in India, especially so far as opium and hemp drugs are concerned, is the religious and social aspects of the problem. Indulgence in opium, on account of age-long usage and custom, is sometimes compulsory on such occasions as marriages, deaths and social gatherings among certain classes. Hemp drugs are considered to be food of the gods and are offered in temples on religious festivals and ceremonial occasions. Some religious sects take these drugs under the belief that they help the individuals indulging in them in freeing his mind from the worldly attractions and in this way concentrate on the deity. This is the reason why in places of religious worship like Benares, Muthra, Puri, etc., there is an enormous consumption of these drugs. Such use of these drugs is, however, rapidly decreasing.

The medical and semi-medical uses of opium and hemp drugs are other important factors. In a vast country like India, where the facilities of medical relief are poor, the majority of the population do not get the benefit of Western medical science. The sedative drugs such as opium and hemp preparations are largely used as household remedies and habits are often formed from such use. The doping of infants with opium can partly be attributed to this. It is still firmly believed by the masses of ignorant classes that opium is a wonderful tonic to the child, it stimulates his growth and prevents the child getting sick. The writer has fully discussed elsewhere the medical and semi-medical uses of opium and the large variety of conditions for which it is used as a household remedy. Almost all the diseases for the relief of which opium and hemp

drugs are used are of minor character. Often the drugs are taken to dry secretions from the conjunctiva and the respiratory tract. Many people suffer from toxæmias of focal sepsis, pains of rheumatic and neuralgic type, mental depression, irritability and hypersensitiveness of the nervous system. These drugs in small doses give them relief and lead to the drug habit.

Treatment of Drug Addiction

The importance of prophylactic measures in preventing drug addiction is appreciated by the medical profession and habit-producing drugs are used with great care. Every physician who treats drug addiction should keep in view that prevention is better than cure. Restriction on the production and sale of the narcotics by the State authorities will not suffice and efforts directed merely towards the suppression of the demand for narcotics are apt to fail. Medical men have been unwittingly responsible in starting addiction in a large number of cases. Every practitioner should see that nobody becomes an addict through his fault and great care should be exercised when selecting hypnotic and analgesic drugs.

It is possible that the abuses of narcotic drugs may be avoided or prevented by giving consideration to the possibility of substituting non-habit-forming drugs whenever possible. When the use of habit-forming drugs is essential, however, care should be taken not to give larger and more frequent doses than are absolutely necessary to achieve the desired end. Patients requiring daily administration of habit-forming drugs should be frequently seen by the practitioner and the amount of drugs ordered or supplied should not exceed that required by the patient. The changes in treatment should be in writing and administration on the part of nurses and other hospital staff should be limited. The patients should not be informed of the name or dose of the drug administered and hypodermic injections should be avoided as far as possible and never self-administered. The use of these drugs should be discontinued immediately when no longer required and if craving has resulted close supervision and appropriate treatment should be maintained until patient is rendered free from the desire.

Treatment of established habit. The true nature of drug addiction and the rationale of its treatment should be thoroughly understood by the physician in charge of the case. The personality of the physician is very important and the patient should be handled very cautiously. The physician should consider an addict as a sick person and not a vicious person with bad morals. Drug addiction is a disease and must be treated as a disease. There is however no specific treatment for drug addiction that will miraculously operate to rid the addicts of their malady. Every possible detail should be studied about the patient's habit so that he may be more accessible to physical and psychotherapeutic treatment. It should be impressed on the patient that he can readily overcome the disease by resolution, patience and self-control. The harsher methods generally fail. The necessity of rest in bed, proper action of the bowels and stimulation of the functions of the kidney and skin are some of the important factors which should not be forgotten before starting the treatment even at the expense of some delay. In addition to the poisonous effect of the drug every addict has to contend with an alimentary toxæmia (of endogenous nature) which is the result of his disordered metabolism. In cases where the treatment is compulsory and in the case of jail patients care should be taken that the addict does not get a secret supply by some underhand means. Other important points to be remembered while treating a drug addict are that the name and dose of the narcotic, if administered out of necessity, should be kept secret. The word 'cure' should not imply merely getting the patient rid of the drug temporarily or permanently by gradual or sudden deprivation of the drug but it should imply his return as far as possible to somatic and psychic integrity, and this desirable state of health is difficult to obtain.

The treatment of drug addiction and especially addiction to opiates can be divided into two phases, involving first the detoxication or physical rehabilitation stage, secondly the emotional stabilisation and re-educational phase.

Detoxication or physical rehabilitation stage. By detoxication or physical rehabilitation is meant the withdrawal

of the drug either suddenly or gradually followed by measures to improve his general health. Various methods to effect detoxication have been discussed by Adams in his review on the treatment of drug addiction. The following methods of withdrawal are in vogue.

I. *The Ambulatory method* is most suitable from the ordinary practitioner's point of view. The patient is free to go about but receives from the doctor or under his instructions such quantities of the drug as are absolutely necessary. The object is to gradually reduce the amount of the drug so that it can either be reduced to a minimum or be completely withdrawn without the least possible discomfort. This method is very popular in India and is often self-practised by the wiser class of opium and alcohol addicts.

II. *Sudden withdrawal method* was at first tried in Germany by Levinstein in 1875. The method consists of withdrawing the drugs from the beginning. The procedure is a very severe and drastic one and has been mostly given up, but it has still some advocates in the United States and in Europe, who favour it with the argument that there is a large psychic element in addition to the physical conditions in the production of the withdrawal symptoms. If the patient is made confident that he is not going to have any more of the drug he will not suffer from such severe symptoms as anticipated. Hence they consider this method quite safe. Scalesh and Kuh (1934) treated 5,000 cases in U. S. A. by this method without any serious withdrawal or asthenic symptoms and had no death.

The Ministry of Health of Great Britain, Departmental Committee on morphine and heroine addiction (1926) after going through all the different methods came to the conclusion that the sudden and rapid withdrawal methods were not satisfactory on the whole because they were only applicable in the case of young and healthy addicts and those who had not been addicts for long periods. They were sometimes dangerous and the permanent results of the sudden method were bad and there was a strong tendency to relapse.

(a) *Sudden withdrawal without special measures.* In its simplest form it means complete cessation of the addicts's ration from the beginning and confinement of the patient to bed under the care of a

skilful nurse. The bowels should be working properly but drastic purgatives should be avoided. Diarrhoea and sickness are treated on general lines. Insomnia is met by simple hypnotics like bromides and paraldehyde. For collapse cardiac tonics like strychnine, digitalin and cardiazol are given. In cases where there is actual danger to the life of the patient give small doses of morphine. For detailed information of this method the reader is referred to the work of Richards, Nelaes and Massee.

(b) *Sudden withdrawal under the influence of hypnotic drugs.* The idea of using hypnotic drugs is to hide the withdrawal symptoms by means of sleep. A large list of hypnotic drugs have been employed by the exponents of this method the most common being paraldehyde, somnifen, luminal-sodium, pernocton, and other barbiturates. The use of these drugs is no doubt attended with some danger. A modification of the 'sleep method' has been described by Meuburger. He employs a light chloroform anaesthesia in the same way as in midwifery cases. The paroxysms of craving are treated in the same way as the pains of child birth and whiffs of the anaesthetic are given from time to time to secure narcosis. The chloroform may be administered from a drop bottle over a compress and administered whenever the patient is under a strong spell of the craving. This method requires close attention by the doctor and the nurse.

(c) *Sudden withdrawal by the aid of drugs of the atropine series.* Scopolamine or hyoscine hydrobromide and atropine are the drugs used in this method. Scopolamine treatment has been tried by Light and Torrance in Philadelphia General Hospital. The patient is at first prepared by being placed on liquid diet for 24 hours. He is given a mild dose of calomel at night to be followed next morning by a saline purgative. He is then given three doses of scopolamine hydrobromide 1/200 gr. hypodermically at 4-hourly intervals and with each dose is given 1/40 gr. of strychnine. A few more injections of scopolamine may be given, the dose being gradually raised to 1/100 gr. and at the end of 36 hours the drug is stopped. When the patient begins to get out of the influence of scopolamine, large doses of phenobarbital are given and if the withdrawal symptoms are still severe and troublesome, a single dose of $\frac{1}{4}$ gr. of morphine may be given. Any further treatment of the case is symptomatic.

(d) *Sudden withdrawal with the aid of specific drugs like narcosan.* Narcosan was first used by Lambert and Tinly in 1926. It is stated to be a solution of lipoids, proteins and water-soluble vitamins. The lipoids are obtained from soya beans and cotton seeds, the proteins from alfalfa seeds or Hungarian millet and vitamins from various plant seeds. The advocates of this drug believe that narcotics such as morphine call forth in the body certain protective substances to neutralize them and when they are suddenly withdrawn these neutralizing substances are themselves toxic to the body and produce with-

drawal symptoms. The lipoids in narcosan are believed to neutralize the toxic substances in place of narcotics. Some of the authorities do not believe that alkaloids can act as antigen. Martin and Williams believe that certain non-specific vegetable proteins in narcosan may stimulate endocrine function. These authors used a preparation from alfalfa proteins combined with ovarian hormone with gratifying results. Recently they have supplemented their protein and sex hormone preparation with adrenal cortex preparations.

(e) *The blister serum treatment of Modinos.* This is another specific treatment which has recently come into vogue. Properly speaking this should be termed as rapid and not sudden withdrawal. The method is very simple; cantharides cerate plaster to a size of 8 sq. cm. and 1 mm. in thickness is applied to the patients' chest or abdomen, and after 16 hours serum varying from 2 to 8 c.cm. is taken and reinjected into the upper part of the arm or leg. The operation is repeated on the 3rd or 4th day, and the 3rd injection is given 4 to 6 days after the second injection. The dose of the narcotic is rapidly reduced and may be completely cut off within 3 to 7 days. It is believed that antibodies are formed which create a distaste for the drug but this view is not universally accepted and the distaste for the drug is attributed to the production of hypersensibility. Other authorities, like Noordhock, consider that the so-called hypersensibility is not specific but is merely psychological and may be obtained by merely injecting common salt solution. He further states that relapses after the treatment are as common as with other methods. Before starting the treatment the urine should be examined for albumin as cantharides may cause injury to the kidneys.

(f) *Sudden withdrawal aided by special drugs like euphyllin, insulin, etc.* Euphyllin and insulin have been credited with the power of alleviating a certain amount of the distressing withdrawal symptoms. Euphyllin has been used on the presumption that morphine withdrawal induces hydration of the blood and probably of the tissues in general. The drug is a powerful diuretic and may be given intramuscularly or intravenously twice a day in 0.48 gm. doses. The injections are given for 3 to 10 days according to the severity of the symptoms.

Insulin treatment. Insulin alone or with grape sugar has also of late been tried on the Continent. Sakel (1930) used insulin alone in doses up to 80 units in 24 hours, to combat withdrawal symptoms in cases where morphine was cut off abruptly with satisfactory results. Braun administered bigger doses of the drug and in addition employed soporifics like luminal. The results of these authors are very encouraging.

III. Rapid withdrawal cure. Rapid withdrawal consists in completely withdrawing the drug in a fortnight. It can be accomplished in the following ways:—

(a) *By the injection of auto-serum* (already described under sudden withdrawal).

(b) *Aided by drugs of the opium series.* Heroine, codeine, cocaine have been tried from time to time especially by the lay people but have invariably resulted in the substitution of a habit of a worst kind. The only drug worth the name is codeine which can be administered during abstinence symptoms in doses of 1 to 3 gr. at 2 to 3 hourly intervals. Lambert also advocates this treatment but he reduces the dose by one tenth every day for 10 days. Codeine is begun on the second day and the dose rises with the decrease of morphine. The initial doses are $\frac{1}{2}$ gr. every 4 hours rising the next day to 1 gr., 3rd day 4 gr. and 5 gr. on the 5th day. The drug is administered in the form of codeine phosphate through the same syringe as morphine. By this plan of giving the drugs together the patient does not know when morphine is stopped and he is getting codeine only. Codeine is then gradually tapered off and saline injections substituted until the withdrawal symptoms are over. The patient does not suffer at all under this method and is quite safe.

(c) *Aided by endocrine preparations.* Liver extract, adrenalin and other glandular products have been employed. Rojas and Belby first tried this method in the Argentine and hence it is known as 'Argentine method.' The dose of morphine is reduced to 10 mgm. within the first 4 to 5 days, then $\frac{1}{2}$ to $\frac{3}{4}$ c.cm. of adrenalin solution (1 in 1,000) is substituted for the drug and it is stated that the patient cannot detect the change. Ephetonin, a therapeutically allied drug to adrenalin has also been tried with success by Bernhardt. These drugs however, should not be used in sympathetico-tonic patients.

(d) *Aided by drugs of the atropine series.* Lambert and Towns used a mixture of belladonna, hyoscyamus and xanthoxylum in the proportion of 2 parts of a 15 per cent. tincture of belladonna and one part each of a fluid extract of hyoscyamus and xanthoxylum. In the beginning 2 drops of this mixture were given at hourly intervals, the dose being gradually increased to the point of tolerance for belladonna. Simultaneously the drug was withdrawn as the condition of the patient permitted. Free action of the bowels was maintained by means of blue pill followed by salines. Post-withdrawal insomnia was combated with a large dose of luminal.

Scopolamine in conjunction with hypnotics is employed by Hahn and others. Twilight sleep methods have been used in Germany.

IV. Gradual withdrawal. This method is suitable for countries like India and has been recommended by the departmental committee in Great Britain. The following are some of the important modifications.

(a) *Without any drug.* It has been already described under the ambulatory treatment.

(b) *With the aid of drugs.* The author has often used with success drugs like belladonna, bromides, nux vomica, etc. These drugs are substituted for opium and administered in the form of a pill and in this way the dose of opium is reduced to nil. In opium smokers the smoking is first replaced by opium by mouth and then the drug is gradually withdrawn with the help of the above mentioned drugs.

(c) *Conditional reflex method.* Charles Rubenstein at Los Angeles sanitarium has recently devised an interesting method. In every case hypodermic injection of morphia was accompanied by the ringing of a bell, but later on massage of the dorsum of the fore-arm for one minute after each injection was substituted. In another case a tuning fork held close to the ear until the vibrations ceased was used as the conditioning stimulus. In each case, after the reflex had been established, injection of sterile physiological saline or water replaced the morphine injection. In both cases it was found that the treatment was rapid and effective and did not produce the so-called withdrawal symptoms.

Emotional stabilisation or re-educational and social re-placement stage. This constitutes a rebuilding of a personality after the drug has been withdrawn because if the character is not rebuilt there will be a relapse. A wise physician will study the causes which led to the addiction and if possible remove them. The patient's general health should be built up both by physical and medical measures. Outdoor life, occupational and diversion therapy and engagement in a hobby are important. Physical and mental fatigue and lassitude should be avoided as they are very often the cause of relapse. Psychotherapeutics are important. In the rebuilding of the personality lies the hope of preventing relapse.

Treatment of Drug Addiction with Special Reference to India

Although in India drug addiction has existed on a more extensive scale than any other country in the world with the exception perhaps of China, little is known regarding the problem. Two commissions were appointed to go into the matter in the end of the last century; a Royal Commission was appointed in 1893 to enquire into the prevalence of opium habit and a commission to go into the question of hemp drugs was appointed by the Government of India in 1895. Both these commissions collected important information regarding the prevalence and effects of these drug habits in a general way, but unfortunately the medical and scientific aspects of these addictions were not inquired into fully at that time. Nearly forty years have elapsed since these com-

missions did their work. Considerable changes have occurred and new drug habits have come into being, yet a perusal of the literature shows that very little work has been done on this important subject. The information available even with regard to the present-day incidence of the drug addictions is meagre. The temperance and anti-opium societies have published some data, but these are biased and often inaccurate and misleading. Even such an important subject as infantile administration of opium, which is still so prevalent, is doing an enormous amount of harm and is probably the cause of the high infantile mortality in this country, has not been systematically investigated. Opium eating is very prevalent in many parts and opium smoking is indulged in freely in Assam and other areas. The hemp drugs are used to an enormous extent. No systematic work has been done to determine the ill-effects produced by these drug habits.

It is not therefore surprising that the medical profession in this country is very ill-informed on the subject of drug habits and their treatment. During the course of his investigations in different parts of the country, the writer has not come across many medical men who had any considerable knowledge regarding the treatment of drug addictions or of the phenomena which accompany abstinence. The general impression appears to be 'once a drug addict always a drug addict'; he is incurable and that is the end of him. Ordinary hospitals generally refuse to admit addicts; mental hospitals are not suitable for many reasons. There are no institutions established anywhere in India and the institutional treatment under expert guidance is unknown. It would certainly be advantageous if a few specialised institutions of the type of abstinence sanatoria were established in areas where the incidence of addiction is very high so that treatment could be carried out on scientific lines. There is no doubt that the public would take advantage of them. The writer's experience so far as the treatment of addictions is concerned is, therefore, limited to the non-institutional methods. From the point of view of treatment, the drug addicts in this country are divisible into three main groups :

I. There is a large group who use opium or hemp drugs in small or very moderate quantities. The majority of these have started the drug after the middle period of their life, generally for some minor disease or ailment. They usually start with a small dose and do not increase it. The narcotic and the euphoric effects of the drug have no attraction for them; indeed these are not produced in this group at all. The *habitués* thus have no temptation to increase the dose, in fact, they fully appreciate the evil effects which would result from it. Most of them are good and successful citizens and carry on their daily work quite efficiently. The writer has known numerous persons who have taken small doses of opium or hemp drugs for 20 or 30 years without any apparent harm. As a matter of fact it would appear that the drug was doing them good as its stoppage made them ill and prevented them from

carrying on their daily vocations of life. It stands to reason that when a person can lead an active and useful life on fixed and unchanging doses, there could hardly be any mental or moral deterioration. Treatment in this large group would appear to be quite unnecessary. Some of this group, however, gradually increase their doses and suffer from the toxic effects of the drug. In such cases only treatment is desirable and is wanted.

II. The next and a very large group consists of those who owe their entry into the paths of addiction to the association with and example of other addicts and to no other reason. Some of these are normal individuals who are anxious to be treated and they respond quite well to treatment. A proportion, however, start the habit from idle and vicious seeking after new sensations; they take the drug for its pleasure-giving effects and for sexual stimulation, and are generally found in large towns. Many of them have a defect of character and their mental make-up and appear to be engrossed in furthering their indulgence and increasing the dose. They also have a tendency to indulge in more than one drug at the same time, *e.g.*, alcohol and opium, alcohol and cocaine; alcohol, opium and hemp drugs. This class of vicious addicts are the most difficult from the point of view of treatment. Fortunately this type, which is more in evidence in Western countries, is not commonly met with in India. The few that exist belong generally to the rich and indolent classes. They do not seek treatment and nothing short of forced confinement in a special institution and prolonged training and reconstruction of character will restore them.

III. There is the third smaller group of *habitués* who have started using the drug in an attempt to tide over a period of special strain or gross over-work and fatigue. This class of addict is the product of large towns and their percentage is not nearly so high in India as in the West. This is the class who are anxious to get rid of the habit, are easily amenable to treatment and do very well even under non-institutional treatment.

Prophylaxis. The importance of prophylactic measures in preventing drug addiction is appreciated by the medical profession in India and habit-producing drugs are used with great care. While an analysis of the histories of drug addicts in Western countries shows that the medical man has been unwittingly responsible in starting addiction in a large number of cases, in India the writer has not come across a single case in which addiction to opiates or hemp drugs could be attributed to their use by the medical practitioners in the first instance. With cocaine and morphine addiction, however, this has occurred quite frequently. In India, where addiction to crude drugs is in vogue and the alkaloid addiction so far as opium derivatives are concerned is uncommon, the importance of prophylaxis by the doctor does not play such an important part as in Western countries. The stringent restrictions imposed by the Government on the distribution and sale of narcotic drugs (opium and

its derivatives and cocaine and its derivatives) have to a very great extent safeguarded the spread of alkaloid addictions. Such drugs are not allowed to be sold except when prescribed by a qualified medical practitioner; the dispensing chemist has to keep a careful account of every grain of the drug sold in books kept for the purpose which are frequently scrutinised by the authorities.

Treatment of Opium Addicts

Sudden and gradual withdrawal. The withdrawal of the drug by the 'sudden method' advocated by Bonhoeffer has been recognised to be scientifically the best method of treatment in many countries. In spite of the success achieved with it in Europe and America it has not been possible to carry it out in India. The writer has tried the method, but has met with little success. The reason is that the conditions under which the cases were treated were far from ideal. There are no specially equipped institutions in this country where addicts undergoing this form of treatment could be housed and could have all the facilities to take them through the critical period of abstinence symptoms. The post-withdrawal insomnia and the digestive and other troubles are extremely distressing and need efficient handling. Some of the writer's cases had to be treated in the wards of an ordinary hospital. Some were treated in their own homes where the success of such a treatment was doubtful from the beginning. The writer's experience, therefore, with regard to the sudden withdrawal method is limited and unsatisfactory from every point of view. Although he has no personal experience of such treatment in special institutions, he has no hesitation in saying that so far as Indian addicts are concerned, the sudden withdrawal would imply a period of frightful physical and mental suffering and trial which the majority of them would be unable to bear. The shock of sudden withdrawal would be too much for many of the addicts and even those with strong will-power and determined to get rid of the habit will stand it with difficulty. It would make the most willing and determined of them lose confidence and they would end by refusing to go through the treatment. Their sufferings would make them lose their faith in the treating physician, and they would become distrustful and hostile so that it would become difficult to establish friendly relations or to inspire confidence in them. The writer has often heard inveterate opium eaters remark that they would rather endure hell than the abstinence symptoms. Experience in India is in accord with those of many authorities in the West who consider that the patients subjected to harsher methods of treatment, such as locking them up and letting them 'suffer it out' are the very ones that are more likely to relapse and go back to the habit. The above remarks apply to the opium addicts only. In the case of hemp drugs, cocaine, alcohol and chloral hydrate, sudden withdrawal can be carried out under non-institutional conditions without any great difficulty.

The writer has met with a great deal of success with the slow or gradual withdrawal method. There is no doubt that whether the process of withdrawal is gradual or sudden, a great deal of suffering has to be gone through by the patient. Administration of no amount of drugs will completely eliminate the distressing symptoms of abstinence. With the gradual method, however, the pain and discomfort of actual withdrawal are reduced to a minimum. If due attention is paid to the psychological side of the treatment, the patient is made to believe that the physician thoroughly understands his trouble and is doing his best to relieve him of his sufferings, the chances of a permanent cure are greatly enhanced. The patient may even carry not unpleasant memories of his restoration period. Another advantage is that the post-withdrawal insomnia, which is an extremely distressing condition, is much less frequent. Moreover under conditions existing in India, it appears to be the method of choice. If the withdrawal is effected with reasonable celerity and with as little discomfort to the patient as possible, it will encourage other sufferers to seek the treatment and those who have relapsed may also return. While it cannot be said how long it will take an Indian patient to be cured if he were to undergo treatment in an institution with the sudden withdrawal method, the experience of many European institutions is that at least three months' stay is necessary. The adoption of such a treatment will, therefore, be very expensive for a country like India. The writer's experience is that with the slow withdrawal method it takes three to six weeks to effect a cure in most of the Indian addicts who are going to be cured. The decrease in dosage is carried out very gradually at first so that it is imperceptible. After a few days it can be effected more rapidly especially if some pill such as that containing *nux vomica*, gentian and black pepper is given as a substitute. The substitution is started with the morning dose at first, leaving the evening dose untouched, this procedure prevents insomnia. Minor symptoms such as diarrhoea, epigastric pain, nausea may be met by giving ordinary alkaline mixtures. Usually in three to four weeks the drug can be entirely stopped.

It cannot be denied that in spite of all precautions a large number of failures result. In many cases when it was hoped that all was going well, it was suddenly discovered that the patient was secretly obtaining a supply of the drug. The ingenuity shown by the addicts in this connection and the extraordinary way in which they evade those on guard, is amazing. The chances of the treatment being prematurely suspended are also great. Even by the slow method the withdrawal cannot be effected except by exercising a good deal of compulsion. Most of the patients start with good resolutions but give in about the second or third day when the symptoms are very acute. To keep control over such patients under ordinary hospital or home condition is very difficult indeed. With full knowledge of all these difficulties the gradual method has been tried under non-institutional conditions with a fair degree of

success, especially in addicts of short duration. Considerable care and attention have to be exercised in the selection of cases. Before starting the treatment the patient must be thoroughly examined and any physical condition which may have led to addiction, *e.g.*, septic foci, etc., must be treated. The duration of addiction is an important factor, cases under 5 to 7 years taking 10 to 15 gr. daily are generally amenable to treatment. In many persons taking over 20 gr. daily for prolonged periods, circulatory disturbances leading to collapse are likely to supervene if the drug is suddenly withdrawn. Sudden withdrawal is successful and is recommended with addicts taking under 5 gr. daily.

The gradual withdrawal method is also suitable for mass treatment of opium addicts. During the Great War in the East African campaign the writer was in medical charge of a Sikh Company of sappers and miners, about 200 strong, from a State from Northern India. Most of the Indian officers and men of this unit were heavily addicted to opium, many taking as much as 100 gr. daily and some over 200 gr. The unit in the beginning brought a certain supply of opium with it, but this was soon exhausted and men had to fall back on the Commissariat supply of 5 to 6 gr. daily. With the help of the Officer Commanding of the Company, the writer had no difficulty in cutting down the dose to a few grains a day, in a month's time, without any of the men showing signs of distress. They gladly went through the cure and some of them gave up the habit entirely. As there were no towns near, the chances of any one obtaining local supplies were completely eliminated.

The writer has shown that there is a predominant psychic element in opium addiction and the production of abstinence symptoms. He has come across cases of persons addicted to large doses of opium (20 to 100 gr. a day) who have been sent to a jail for some criminal offence and their supply was inevitably stopped, they did not however suffer from very marked symptoms of abstinence. Even in severe cases of morphine addiction many of the mental symptoms such as agitation, anxiety, persecutory ideas, psycho-sensory disorders, mania, even hysteriform or epileptiform attacks, present all the features of an acute psychosis. During the treatment of addicts to rid them of opium habit, the drug can be largely or totally replaced by substances such as gentian or nuxvomica in pill form without the patient realising it. Further if the patient is not aware that he is taking opium, the drug can be effectively given for weeks or months for its therapeutic effects, without producing addiction or abstinence symptoms. A great deal can be done by getting the co-operation of the patient and proper attention to the psychological side of the treatment ensures success in many cases.

Infantile administration of opium. The habit in infants and children is not difficult to break. In the usual course of events the parents continue to give the drug up to the age of two or three years and then when the child can take care of itself it is stopped. Both the gradual and sudden methods of withdrawal have been tried with equal degree

of success, but it is better to adopt the sudden method. The psychological element plays a very minor part in children and as a rule there is little discomfort. The withdrawal symptoms met with are looseness of the bowels and irritability of temper, and in severe cases loss of appetite, nausea and abdominal pains also occur. Diarrhoea can be easily controlled by powders containing sodium bicarbonate, bismuth carbonate and aromatic chalk. In severe cases with mental irritability a bromide mixture with a few minims of tincture of belladonna may help to quieten the patient. The child gets quite well in a few days and a cure is effected, no after-treatment is, as a rule, necessary. Even the worst cases with marasmus and emaciation begin to put on weight soon after they are rid of the habit.

Opium-smoking. The experience in India is that opium-smoking is more difficult to cure than opium-eating. Fortunately, owing to very strict regulations the habit of smoking opium is now rapidly disappearing from many parts though it is still prevalent in Assam. The writer's experience of its treatment is very limited, but there appears to be little doubt that an opium smoker is much more attached to the drug than an opium eater. It would appear that although smaller quantities of the alkaloids are absorbed (most of them must be destroyed by heat), the absorption is very rapid from the large surface of the capillaries of the lungs and the respiratory tract, and the effects are sudden and more intense resembling an injection of morphine. The treatment of opium-smoking has not been properly worked out in India. Some authorities allow the patient the drug by the mouth and gradually cut down smoking. Once eating is successfully substituted for smoking the addict becomes more amenable to treatment.

Addiction to 'post' (unlanced capsules of P. somniferum). The common belief among the addicts is that *post* does less harm than opium. The writer's experience, however, is not in accord with this view. A person addicted to poppy heads requires comparatively much larger doses of opium to produce a similar effect; moreover the physical and mental effects produced by ordinary doses of *post* are much more marked than with moderate doses of opium. This, in all probability, is due to the potentiating effects the constituent alkaloids of poppy capsules have for one another. It is more difficult to get rid of this habit than the opium habit. The sudden method is rarely practicable in these cases, the gradual method being the only one which meets with success. The dose is gradually reduced by half a capsule till a fourth of the original dose is reached and then it is stopped entirely.

Auxiliary treatments. Atropine and hyoscine have been tried in the earlier stages of withdrawal of opium and strychnine in the later stages with good results. The belladonna hyoscyamus mixture recommended by Lambert is useful in that it lessens the shock, decreases diarrhoea and relieves insomnia. Gastrogenous phenomena are not marked in the treatment of the opium habit as they are with morphine, and alkaline and

acid treatments are not necessary. Adrenalin and ephedrine have been tried for mitigating the withdrawal symptoms in a few cases with good results. It is rarely necessary in this country to use sedative drugs such as cocaine, narcozan, luminal, sodium amytal, pernocton, etc., in the gradual withdrawal treatment of opium eaters and the writer has no experience of the use of these drugs. He has used insulin with success in a number of opium and morphine addicts. So far as opium eating is concerned he has carefully tested the effects of the drug on the blood sugar of both diabetics and normal Indians. Small and moderate doses of opium have little or no effect on the blood sugar of individuals who are not suffering from disturbances in carbohydrate metabolism. In persons whose blood sugar content is abnormally low, opium may raise it. The blood sugar in the early and mild types of diabetes may be reduced and it is only in the severe forms of the disease that the blood sugar is actually raised. In some patients opium does no more than raise the renal threshold of excretion. The writer's findings with regard to opium agree with those of Simenauer, Pulfer and Anton who found that in human beings as opposed to animals, morphine produces little or no disturbance of the carbohydrate metabolism.

The utility of diuretics such as novasurol and ephyllin in slow withdrawal method is doubtful. The writer's observations show that in addicts taking moderate and large doses of opium there is retention of fluid in the blood; in those taking small doses, however, the output of urine is actually increased and the blood fluid is not altered. When the kidneys are damaged and there is albuminuria the administration of 1 to 9 gr. of opium daily produces an appreciable decrease in the quantity of urine passed and in none of the cases were there indications of added damage to the kidneys which the drug is reputed to do in such cases.

Vesicatory serum therapy in opium addiction. Although the writer's own experience with this form of treatment is limited, but the method is being tried in the treatment of opium addicts in Burma jails. Opinion among the medical officers trying the treatment is unanimous on one point, namely that one or more injections of the autoserum from a blister make the addict sensitive to opium. The patients say that they do not wish to take opium any more, not because they do not like it, but because the consumption of the drug even in large quantities does not produce the pleasure or exhilaration that it used to produce before. On the contrary the effects produced by a dose are unpleasant, and heaviness of the head, nausea, vomiting, etc., are produced. A distaste for the drug is thus developed and as euphoric effects are not produced opium is not wanted. A control experiment was also tried in the following manner. Some addicts were blistered in the usual way and the fluid from the blister was removed. Instead of the fluid from the blister being injected, in a number of cases injections of normal saline were given. It was found that the addicts who had normal saline did not respond in the same

way as those in whom actual serum was injected. In other words, mere blistering did not do any good so long as the serum was not reabsorbed, nor were the effects due merely to the psychological effects of the injection. It is at present difficult to say how long the sensitiveness to the drug of addiction will last, but investigations on this subject are being carried on. It must be remembered, however, that most of the addicts were prisoners under prison discipline and living under conditions in which temptations by way of easy access to opium did not exist. In one of the jails the treatment was tried on two warders who were free to go about and could easily obtain opium if they so desired. In both cases the injections of serum produced the same effects as in the prisoners.

Whether the treatment will eventually produce a permanent cure or not is difficult to say in the present state of investigation but the results so far obtained are certainly striking. The patients gained in weight after the treatment, the appetite returned and the general health improved in a remarkable manner. The following provisional conclusions can be drawn from the data so far obtained:—

(1) That the treatment with vesicatory serum injections is a valuable measure in the treatment of opium addicts.

(2) That probably addicts who have any will-power left will be completely and permanently cured of the habit through its agency.

(3) That probably those who have no will-power left, although they may be temporarily benefited, will relapse as soon as they have the opportunity.

It is believed that about 50 per cent. of addicts could be cured by this method.

Lecithin treatment. Lecithin treatment of opium addicts has been mentioned by Ma (1932) and is being tried in India by the author. From certain observations made on the physical properties of the blood sera of such addicts, it has been found that the protein contents, specially the neuro-proteins, are lacking or deficient, particularly during the withdrawal period. Ma (1931) from a cytopathological study of chronic morphinism in albino rats found that the withdrawal of the drug in the addicted animals leads to severe pathological conditions of the Golgi apparatus in the cells of various organs. Without treatment these conditions are overcome in 10 to 12 days. Feeding with lecithin, on the other hand, for a period of six days before and for some days after prevented Golgi apparatus from becoming abnormally reduced and was accompanied by a condition of general well-being of the animal which was absent in those receiving no lecithin. The treatment has been tried in China on 143 opium-smokers. In addition to their ordinary diet the patients are given 6 to 9 eggs per day to enrich the diet in lecithin. The bouts of craving are overcome by the administration of tincture of opium in small doses. The lecithin given is

prepared from eggs and made into pill with glycyrrhiza powder, the usual daily dose being 4 to 6 gm. Lecithin obtained from soya-bean has been used in China in the treatment of addiction to opium. It is administered by the mouth in doses of 60 to 90 gr. daily and said to produce a spontaneous and gradual discontinuity in the use of the drug by the addict. The administration of lecithin is discontinued a few days after the complete stoppage of opium. No discomfort is noticed and no abstinence symptoms are produced.

Hemp drugs. The treatment of hemp drug habit is not at all difficult, though it is easier to cure the eating habit than the smoking habit. The withdrawal symptoms as they are met with in case of opium addicts are hardly ever seen, indeed the patients find no difficulty in giving up the habit of their own accord. In Northern India many people indulge in 'bhang' drinking in the hot weather on account of its cooling and refreshing effects and give it up in the winter quite suddenly. Hemp preparations when taken habitually by the mouth can be suddenly withdrawn without any marked untoward symptoms. Temporary loss of appetite, constipation lasting for a few days and rarely palpitation and restlessness may occur, all these can be easily dealt with.

Charas and ganja. These are stronger preparations and as these are generally indulged in by smoking, their effects on the system and particularly on the nervous system are more pronounced. The will-power of the smoker is weakened and without the physician's help he is not able to give up the habit. Treatment in special institutions with facilities for forcible withdrawal is likely to give the best results. The psychological and mental treatment and training and education of the addict are as important in case of hemp drug smokers as opium addicts, in spite of the fact that considerable physical pain accompanying withdrawal is absent.

Cocaine. The habit of eating cocaine is easier to cure than that of injecting cocaine. Removal of the addict from the environments in which he has learnt the habit and from associates in whose company he indulges in the drug, preferably to a place where he cannot get it, often effects a cure. The writer knows of many instances where the individuals from one part of the country went for a few months to another part where they were unable to get the drug and where there were no associates; they were able to conquer the craving for many months at a time without difficulty. When, however, they returned to their old surroundings they again succumbed to the temptation. Similar facts have been observed in addicts who have been kept confined in prisons. They are able to give up the habit during confinement and go for years without the drug; they generally take it up again after discharge. The writer is convinced that cocaine eating is comparatively a much milder form of indulgence than cocaine injecting.

Psychotherapy and mental training are important; the psychological rearrangement of the personality by finding some innocent emotional

compensation will often help the habitue to give up the habit. The drug must be withdrawn all at once and symptomatic treatment given for the withdrawal symptoms. Next to the opium habit, the cocaine habit is the most difficult drug habit to cure in India.

After treatment. The importance of psychological aspects of the treatment of drug addicts has already been stressed. The responsibility of the physician does not end after the drug is withdrawn. The period following the withdrawal is most critical and dangerous and unless great care is taken relapses will occur. The whole of the nervous system has been strained and a thorough reconstruction and rehabilitation of the personality and the character of the addict are imperative if a permanent cure is desired. The physician can do much by way of encouraging the patient and making him believe that by his will-power and firmness he will get rid of the habit. A common belief among Indian addicts is that elimination of the drug habit will leave them sexually impotent. There is no basis for such a belief and the patient should be fully assured that the loss of sexual desire which they observe after giving up the drug is a temporary phenomenon and is a part of the general loss of tone of the organs. It passes off in 4 to 8 weeks but rarely it may last for several months. During the period following withdrawal a good tonic in form of iron, arsenic and strychnine is very helpful. Occupation therapy is also very important. As soon as possible the patient should start doing some work so that his attention is diverted in other directions. He must lead a quiet life and avoid excesses of all kinds for a year or more after withdrawal has been successfully effected.

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PART VI

DISEASES OF THE SKIN

Anatomy and Physiology of the Skin. The skin or integument is an integral part of the body and is in close relationship with the subjacent structures through its connective tissues, blood vessels and nerves. It can be considered as an elastic covering of complex structure with certain independent physiological functions and bearing specialised appendages, namely, the hairs and nails. Structurally, the skin consists of three principal layers, the epidermis or cuticle, the dermis or corium which is the true skin and the subcutaneous tissue.

The *epidermis* or *cuticle* is the outer superficial layer which is waterproof and protects the underlying delicate structures like fine blood vessels and nerves from external injuries. It is composed entirely of epithelial cells of squamous and cuboidal type and is devoid of blood vessels or capillaries. Depending on the situation and thickness, the epidermis is formed by three to five layers of cells which are termed from above downwards, *stratum corneum*, *stratum lucidum*, *stratum granulosum*, *stratum Malpighii* or the *rete mucosum* and the *stratum germinativum* or basal cell layer. It is from the basal layer that all the other layers originate.

The *stratum corneum* or horny layer is the outermost and varies in thickness in different parts of the body. It is thickest on the palms and soles, intermediate on the scalp and thinnest on the eyelids, face, prepuce, webs of the fingers, flexor aspects of the elbows, groins and sides of the tendo achillis. The cells in this layer do not possess nuclei and are flattened and dry near the surface. These cells are keratinised and are partially impervious to water owing to the presence of a waxy substance. The *stratum lucidum* occurs immediately beneath the horny layer and is seen in microsections as a thin, even, colourless, translucent band. It is composed of one or two layers of irregular distended cells with vestigial nuclei. The *stratum granulosum* is the next deeper layer and is composed of one or more flattened coarsely granular cells with shrunken nuclei lying in vacuole-like spaces. This layer is very thin or absent in the fine skin at the webs of the fingers etc. The *stratum Malpighii* or the rete is also known as the prickly cell layer and comprises of a varying number of polygonal cells distributed in a 'mosaic pattern.' The cytoplasm is spongy and the cells, all of which show definite nuclei, are united to each other by delicate protoplasmic processes—the prickles. In the upper regions these polygonal cells are more or less flattened and in the neighbourhood of the basal layer they are somewhat elongated. The *stratum germinativum*

or basal layer consists of a single row of cuboidal cells arranged vertically to the basement membrane separating the epidermis from the corium. The nuclei are large, oval and centrally situated and show mitosis. These cells contain melanin pigment to which the colouration of the skin is due.

Although the entire surface of the skin appears to be smooth and regular, it is in reality traversed by numerous ridges and furrows distributed according to the folding and stretching to which the skin is subjected during movement. Fine lines exist over the entire surface of the body. On the flexor aspects of the fingers and toes the distribution is more regular and of a pattern characteristic to the individual. The epidermis is anchored to the dermis by means of fine fibrils originating from the corium.

The *corium* or *dermis* is the true skin which, like the epidermis, also varies in thickness in different situations, being thickest on the palms and soles, and thinnest on the eyelids, webs of the fingers and toes, etc. It is anatomically considered as being composed of two strata, namely, the *pars papillaris* and the *pars reticularis* and is richly supplied with blood vessels, nerves and lymphatics. The *pars papillaris* or the superficial stratum consists of round or oval cone-like projections resting on an irregular ridge-like formation in the connective tissue and extends from the basal layer of the epidermis to the level of the sebaceous glands. The *pars reticularis* or the deeper stratum which is composed of interlacing bundles of dense fibrous tissue, commences at the level of the sebaceous glands and merges into the superficial fascia of the subcutaneous tissue. Strands of voluntary and involuntary muscle fibres are found in the *pars reticularis*; of these, the striped muscles occur only in the face and neck while unstriped muscles are more numerous in the scrotal and perineal regions, in the areola of the nipple and on the scalp. Arrector pili muscles originate from the inner sheath of the hair roots, and run obliquely to be inserted at the base of the *pars papillaris*.

The corium is supplied with *blood vessels* situated at four different levels where they form plexuses. The deepest of these plexuses is formed in the subcutaneous tissues. The arterial side comprises of a richly anastomosing irregular network of tortuous vessels which send off branches to form the second plexus about the level of the sweat glands. Extremely fine twigs of arterioles are sent off from the second plexus to form arborising networks in the upper portion of the dermis especially around the sebaceous glands and hair follicles. Some of these fine twigs pass upwards and form the subpapillary plexus with regular oblique meshes from which fine capillaries pass into the tips of the papillae. These capillaries do not anastomose. The walls of the papillary capillaries and the arterioles of the subpapillary plexus consist of a single layer of endothelial cells. The venous return is from a single papillary venous capillary to the subpapillary venous plexus which lies just below the papillae, and anastomosing freely, forms a regular network of

even-sized vessels. Two more venous plexuses are seen, one in the cutis and the other in the subcutis, and are composed of large veins supplied with valves. Control of the capillaries depends on the activity of the suprarenals and the pars posterior of the pituitary, and the permeability of the endothelial wall varies directly with the calcium content of the blood. These plexuses respond to external and internal stimuli in various ways and the resulting clinical phenomena depend on three factors, namely, (a) dilatation or (b) constriction of the capillaries, arterioles or venules with (c) increased permeability of the capillary endothelium or the endothelium of the subpapillary plexus. For example, the first effect of cold is pallor which is due to constriction of the capillaries but dilatation of the deep arteries. During the second stage, the arteries and arterioles contract and the veins dilate giving rise to blueness of the skin. In the third stage there is occlusion of the arteries and stasis in the veins with erythrorrhexis resulting in gangrene. If recovery takes place in the second stage, there is dilatation of the papillary capillaries with exudation of serum into the prickle cell layer and consequent formation of blisters.

In the epidermis there are no *lymphatic vessels* with distinct endothelial wall but numerous intercellular spaces are seen between the cells of the different strata. In the papillary portion of the corium a plexus of fine lymphatic vessels accompanies the blood vessels and drains the lymphatic spaces of the epidermis. A large number of lymphatic spaces also occur in the corium, so much so, that the connective tissue bundles, muscle fibres and the coil glands seem to 'float in distended lymphatic spaces.' A second coarse plexus of lymphatics is found in the deeper portions of the pars reticularis of the corium where the distribution follows the deep blood vascular plexuses. Anastomosing branches are sent off from both these lymphatic plexuses which supply and drain all the structures in the corium.

The *sensory nerve fibres* of the skin are of both medullated and nonmedullated kind. The medullated fibres pass upwards through the subcutaneous tissues along with the blood vessels. The medullary sheath is generally lost at the level of the pars papillaris where the fibrils form irregular network and send off extremely fine twigs upwards between the cells of the epidermis as far as the stratum lucidum. A large number of medullated fibres terminate in the tactile corpuscles, end bulbs and Paccinian corpuscles which are situated on the tips of papillae just below the epidermis. The connective tissue coats of the hair follicles are also supplied by fibrils of medullated nerves. The non-medullated fibres which are derived from the sympathetic ganglia supply the voluntary and involuntary muscles of the skin.

The subcutaneous tissue varies in thickness and density in different parts of the body and is composed mainly of irregular lobules of fat distributed in a fibrous network which supports the blood vessels and

nerves. The superficial fascia forms a resilient base for the whole thickness of the skin to rest upon.

The entire thickness of the skin is pierced by the ducts of the sweat glands and by hair follicles. Both the sweat glands and the hair follicles are placed deep in the subcutaneous tissue, the sebaceous glands which accompany the hair shafts occur in the deeper portion of the *pars papillaris*.

The *sebaceous glands* vary somewhat in structure from a simple saccular to a multiple racemose gland. Their size bears no relationship to the size of the hair follicles with which they are connected, the smallest glands are found in the scalp and the largest in the *mons veneris*, scrotum, nose and external ear. Meibomian glands in the eyelids and Tysonian glands on the glans penis are modified forms of sebaceous glands. Sebaceous glands are found in the corium on all parts of the body except the palms and soles and the terminal phalanges.

The *sweat glands* are situated in the superficial portion of the subcutaneous tissue and consist of a single tube of almost uniform calibre wound into a globular mass. They are found on all parts of the body except at the margins of the lips, on the glans penis and on the inner side of the prepuce. Largest number of sweat glands occur on the palms and soles and fewest on the back and buttocks. The circum-anal, ciliary and ceruminous glands are modified forms of sweat glands. The duct passes upwards spirally through the corium but at the interpapillary portion of the rete this regular spiral appearance is lost. The corkscrew-like course is again resumed at the level of the stratum granulosum and its termination on the surface is marked by a minute funnel-shaped depression in the skin.

The hair. These are horny, pigmented, cylindrical outgrowths derived from the epidermis and having their roots firmly fixed to pouch-like depressions in the deeper portions of the corium. They occur on all parts of the body except the palms and soles, the terminal phalanges and the penis. Three kinds of hair are found on the human body, namely, (i) soft or lanugo hairs which have thin minute shafts and grow on the forehead, limbs, trunk and ear; (ii) long hairs occurring on the scalp, beard and moustache areas, pubes and axillæ; (iii) stiff bristly hairs of the eyebrows and eyelashes. Straight hairs are cylindrical while curly hairs are somewhat flat and ribbon-like and are oval in transverse section. The root is enclosed in the hair follicle which has three layers. The external and middle coats are formed by fibrous connective tissue and are supplied with blood vessels and nerves. The inner coat is structureless and homogeneous and does not contain any blood vessels and nerves.

The nails. These are flat horny outgrowths of the surface epithelium covering the dorsal surface of the terminal phalanges of the fingers and toes. The body or visible portion consists of flat translucent horny cells growing from the sub-nail rete and resting on the nail bed in the corium. The root is firmly embedded in a pocket-like recess formed

by an infolding of the epidermis. The proximal white portion is the germinating matrix, the intermediate pink portion is the nail proper and the distal yellow portion is the dead area which is pared off periodically. The rate of growth varies with age and the season of the year being most rapid in young adults and during the summer months. The finger nails grow faster than the toe nails.

Functions of the skin. (1) *Protective.* The horny layer being keratinised and impervious to water acts as a barrier to bacterial infection of the subjacent structures. This function is subsidised by secretion of the sebaceous glands which keeps the surface epithelium in a pliable condition. Protection against mechanical injury is afforded by the firmness and elasticity of the corium and the fatty cushion-like structure of the superficial fascia on which they are resting. The vulnerable points in the skin are the pilosebaceous orifices through which bacteria gain access to the deeper tissues.

(2) *Sensory.* The entire body is kept cognisant of its change of environments through the sensory nerves of the skin. The special end-organs transmit sensation of heat, cold, pain, pressure and tactile discrimination. The hair follicles are liberally supplied with sensory fibres and hence they also function as effective tactile organ.

(3) *Regulation of heat.* This is done by radiation and evaporation from the entire surface of the skin through the activity of the sweat glands and dilatation and contraction of the blood vessels. Heat or cold may act either directly on the involuntary muscle fibres of the vessels or indirectly through the vasomotor system. Heat produces dilatation and thereby more heat is radiated owing to a brisk circulation. Cold produces contraction of these vessels and radiation from the body is less owing to retarded circulation.

(4) *Secretory.* (a) *Sweat.* A fair amount of water is constantly lost from the body as insensible perspiration which keeps the skin soft and moist. The activity of the sweat glands is under control of the central nervous system and is influenced by atmospheric conditions such as temperature and humidity and various physical states such as emotion, exercise and nausea. The sweat glands are not much influenced by changes in the chemical state of the blood as the kidneys are. Sweat proper is an important factor in the regulation of the body temperature, especially in bringing down the temperature of febrile or other toxic conditions. Excretion of nitrogenous and other waste products is negligibly small as sweat proper consists of about 99 per cent. of water with certain amount of sodium chloride, phosphates etc., in solution or suspension. The composition and consistency vary according to the region and duration of sweating, the secretion of the axillary and circumanal glands being thick and oily. The reaction is always acid and thus affords a protection against multiplication of bacteria on the skin.

(b) *Sebum*. It consists of an oily semi-fluid material composed of fat, fatty acids, salts, cholesterin, albuminoid substances and water. A certain amount of fatty degenerated cellular debris is mixed with it. The secretion varies in quantity according to the situation, being most abundant on the face, sides of the nose, scrotum and the areolæ of the nipples. The production of sebum is slow and continuous and is affected to a certain extent by the vascularity of the skin but the activity of the glands is controlled by the gonads. The principal function of sebum is to lubricate the hair shafts and prevent them from becoming too hard and brittle or too easily saturated with moisture. It also prevents too rapid and undue loss of heat from evaporation by forming a thin spreading film of oily substance on the skin.

(5) *Absorptive*. The horny layer is totally impervious to water or alcohol but fatty substances are absorbed to a certain extent. The degree of absorption depends on the volatile property of these fats or oils at the low temperature of the body heat. Absorption can take place readily through the papillæ if the skin is abraded.

(6) *Nutritive*. The fatty subcutaneous tissue of the skin acts as a store of nutrition in case of emergency and need. Nearly one fifth of this lipid substance is present as free cholesterol which is activated by ultraviolet light and thereby exerts its antirachitic effect.

(7) *Respiratory*. A certain amount of carbon dioxide and a fairly large quantity of water is exhaled from the surface of the skin.

(8) *Melanin pigment*. The colour of the human skin is due to the concentration of melanin pigment in the basal layer of the epidermis. There are certain specialised cells called melanoblasts situated in the upper layer of the corium, which elaborate melanin from the end products of digestion of vegetable proteins especially those derived from the leguminous plants. Under normal conditions the colouring matter is secreted by the melanoblasts as an achromatic substance, and during its drift upwards towards the surface, it is oxidised and stored in the basal layer as the dark russet-brown melanin. Here its principal function is that of a light filter to protect the fine capillaries anastomosing in the papillæ from the injurious effects of strong sunlight. The activity of these melanoblasts is controlled by the internal secretion of the suprarenals and anterior pituitary and hence the basic factor in the colouration of the skin is racial or hereditary. The colour of the hair and iris is also a racial character for the same reason. The essential difference between a dark negroid and a very light Caucasian type of skin is not so much due to the numerical distribution of the melanoblasts (in fact, the negroid skin may show as many melanoblasts in a given area in a microsection as a Caucasian skin) but to the relative capacity of the basal cells to completely oxidise and store the precursor of melanin substance derived from the melanoblasts.

Diseases of the skin may be produced by purely external causes acting on the surface of the integument, or the cause may be internal, the manifestation on the skin being only a reflection of the internal disease. The external causes can be considered under the following heads: (A) Parasitic, (i) animal parasites, (ii) vegetable parasites. (B) Physical agents.

External Diseases Produced by Animal Parasites

SCABIES OR THE ITCH. This disease is caused by the gravid female '*Acarus scabiei*,' burrowing into the epithelial layer of the skin where it consists of two layers only, namely in the webs of the fingers, at the wrists, around the navel and the nipples, on the penis, buttocks, folds of the axilla and between the toes. In very young children, the lesions may be generalised affecting the palms, soles, face and the scalp owing to the skin being thin and tender all over the body. The tunnel produced by the burrowing parasite is utilised for laying eggs and the larvæ which are hatched leave the tunnel by tearing through the roof, thus keeping up the infection by invasion of fresh areas. There is violent itching—hence the name 'the itch'—which is worse at night. The abrasions produced by scratching are very often infected secondarily with pyogenic cocci and the entire clinical picture may be changed thereby. This is especially noticed in the case of babies. The infection is transmitted by direct contagion and is almost always associated with lack of personal hygiene. The disease is often found among the inmates of boarding houses and schools. Instances of infection in people of very cleanly habits are occasionally seen.

Treatment. Sulphur in all forms is the specific. Where there is extensive secondary infection, it should be treated first with cooling lotions, *e.g.*, calamine lotion or weak antiseptic lotions, *e.g.*, acriflavin lotion (1 in 3000), etc. When the inflammation has subsided, intensive sulphur treatment should be given. In straightforward cases treatment consists of scrubbing with a hard nail brush, soap and hot water in the morning to open up the burrows, followed by sulphur ointment (B. P.) which should be rubbed in and kept on for at least 4 to 6 hours. The scrubbing and application of ointment is to be repeated before retiring at night. All clothes next to the skin, bed sheets, pillow cases, counterpanes, etc., should be sterilised by boiling every day; if this is not feasible, the patient is kept without a bath and his clothes, linen, etc., are not changed for 3 days and on the 4th day everything is sterilised by boiling for one hour. The patient is given a good bath with soap and hot water. Some people are intolerant to sulphur and begin to show signs of sulphur dermatitis early in the course of treatment. β -naphthol ointment (10 gr. to 1 oz.) or balsam of Peru ($\frac{1}{4}$ to 1 dr. to 1 oz.) are two of the best substitutes in such cases, but the latter, if used in too concentrated solution for a long time, produces

general toxic symptoms. Sometimes sulphur dermatitis is brought about by the specific treatment being prolonged unnecessarily by the patients themselves as they think that the irritability of the skin caused by the sulphur is due to persistence of the infection. The patients and their relatives should therefore always be warned not to continue the intensive treatment after the 4th day. Growing children may develop allergic dermatitis and this condition should be carefully differentiated from actual scabies and treated accordingly. Prophylaxis is of great importance in preventing a relapse. As a rule more than one member of a family is affected, and unless all of them are treated at the same time, a complete cure cannot be established. Sulphur and camphor dusting powder (sulphur ppt. 2 dr., camphor 2 dr., zinc oxide 1 dr., boric acid $\frac{1}{2}$ dr., starch 3 oz.) sprinkled lightly on the body after bath and on the bed linen at night, is a very good prophylactic agent.

Danish method of treating scabies. The patient is stripped, his clothes are fumigated and Vlemminckx's solution is painted on with a brush. The patient is given a bath with soap and hot water after two hours. This solution is prepared as follows: quicklime 1 oz., sulphur ppt. 2 oz., water 15 oz., boil in earthenware vessel till reduced to 10 oz.; let it stand for some time and decant off the clear sherry-coloured supernatant fluid.

PEDICULOSIS (Lousiness). Three types of the parasite are met with, namely, *P. capitis*, *P. vestimenti*, and *P. pubis* (crab louse).

P. capitis affects the scalp and is spread by direct contagion in schools and boarding houses and from the use of infected hair brush or sleeping with an infected bed fellow. The adult louse causes a good deal of irritation of the scalp and is often associated with *seborrhœa oleosa* of the skin. Secondary infection of the nature of impetigo is not uncommon, and a certain amount of matting and falling of the hair is always noticed, especially in girls who wear their hair long. In persons of cleanly habits it is a transient infection, but in people in whom a head-bath or shampoo is only a luxury it may go on for years and produce actual alopecia. *P. capitis* in long standing cases may invade the body hairs as well. The eggs are laid on the hair shafts and are called nits. For the adult lice, kerosine oil acts more or less like a specific. The hair should be soaked well with kerosine oil, kept on for half an hour and then washed off with soap and warm water. This treatment should be given twice a week, and in the interval, antiseptic hair lotions—resorcin 30 gr. to 1 oz. or β -naphthol 20 gr. to 1 oz.—should be applied night and morning to destroy the nits. All matted hair should be clipped off.

P. vestimenti or the body louse lives on the clothes and only draws its food supply from the human host by sucking his blood. The only way to a radical cure is thorough disinfection of all clothing by steam and hot ironing and strict personal hygiene. It is spread by direct contact.

The parasite is considered by entomologists to belong to the same species as *P. capitis*.

P. pubis affects the pubic hair in both sexes and in men may sometimes affect the hair on the abdomen, chest, axilla, even the eyebrows and eye-lashes. The bite causes intense itching and the parts affected become almost eczematous owing to the abrasion and drying up of serous exudate. It is usually transmitted by intercourse although in rare instances the infection has been picked up from a closet seat. The treatment consists of shaving all the affected parts and burning the hair, a 10 per cent. calomel ointment or β -naphthol ointment, 10 gr. to 1 oz. being applied afterwards. On the eyebrows and eyelashes (which the sufferer usually refuses to shave or clip off) 0.5 per cent. yellow ointment (ung. hydrarg. oxidi flavi) is used.

CREeping ERUPTION. It is caused by larvæ of insects or nematodes burrowing under the skin and producing lesions which are raised above the general surface, linear or gyrate in character, and may be either continuous or broken with bead-like vesicles. The commonest type of lesion is a slightly raised thread-like erythema which is pronounced at its extending part and fading away at the older part traversed by the larvæ. Creeping eruption due to hookworms is seen amongst labourers in plantations and gardens where the hookworm larvæ are rather plentiful in the soil and gain entrance through the unprotected skin of the feet, the commonest sites being between the toes, the thin skin by the sides of the tendo achilles or less commonly on the dorsum of the foot. The larva migrates mostly at night and causes good deal of irritation; scratching opens up the burrows which become infected with pyogenic cocci giving rise to secondary impetigo or weeping eczemas.

Treatment. Cleaning up the sores with fomentations or baths in weak lysol (15 to 20 drops to a pint), and application of calamine lotion or ammoniated mercury ointment as the nature of the secondary infection requires. In uncomplicated cases without secondary infection best results are obtained by cauterising the area around or just beyond the advancing part with carbolic acid and dressing with weak perchloride of mercury lotion (1 in 8000). Another effective method is freezing with an ethyl-chloride spray.

External Diseases due to Vegetable Parasites

RINGWORM OR DERMATOPHYTES. Two varieties are recognised, viz., (1) those that affect the hair and hairy areas alone; and (2) those that affect the smooth skin. In the first group are included:

I. Genus *Achorion* (species *schoenleinii* and *actoni*) which causes favus. II. Genus *Microsporum* (species *audouinii*) which gives rise to ordinary scaly ringworm of the scalp. III. Genus *Trichophyton*, ectothryx and endothryx varieties. The ectothrices cause suppurative lesions of hair follicles, and infect the outer side of the hair shaft; the

endothrices, on the other hand, infect the medulla of the hair shafts which break off flush with the level of the skin with slight scaling of the epidermis.

Ringworm of the scalp. Infection with fungi of the *Achorion* group causes *favus*. The lesions are characterised by multiple, sulphur-yellow cup-shaped crusts, called scutula, each of which is pierced by a hair shaft and emanating a characteristic mousy odour. They vary in size from a pin's head to a large coin and are sometimes imperfectly formed, appearing as grayish or yellow specks scattered throughout the scalp. Contiguous scutula often coalesce at the margins and give rise to fairly extensive patches with thick yellowish adherent scales. The disease may spread on the glabrous skin of the body where the lesions are of fairly large size, discoid in shape and covered with thick yellow crusts. The nails may also be affected. The hairs of the affected area become dry, wiry and lustreless and ultimately fall off. Suppuration occurs in most cases followed by scarring of the skin and consequent permanent alopecia. The scars are white and depressed and the skin appears smooth, thin and glossy. Subjective symptoms are trivial or entirely absent. The disease is contagious and is spread by direct contact in schools and boarding houses. The infection may sometimes be picked up from a barber's shop and no age is exempted.

Ordinary *scaly ringworm* of the scalp, caused by infection with fungi of the *Microsporum* group, is a disease of childhood and is rarely seen after puberty. Both male and female children are almost equally affected. The lesions which are always multiple, begin as small, red, scaly papules, perforated by the hair shafts which become loose, dry, lustreless and break off just above the surface of the skin. The spread of the disease is slow with a tendency to involution in the centre and extension at the margins giving rise to patchy areas of partial baldness with reddened hyperæmic bases and covered with whitish or grayish scales. Typical cases present 'picket' area appearance of the scalp. The lesions do not suppurate as a rule and the alopecia induced by the infection is never complete.

The ectothryx variety of *Trichophyton* produces fairly deep-seated infection of the hair follicles and is accompanied with suppuration and inflammatory changes in the corium. The distended follicles stand out as small, red, tumour-like beads bearing the loose hair shafts which drop off very soon, leaving dilated gaping orifices discharging pus or seropurulent fluid. Several contiguous lesions may coalesce to form fairly large masses—the kerions—which are characterised by rounded, boggy, carbuncle-like tumours of fairly large size with numerous sieve-like openings through which pus can be squeezed out. There is intense inflammatory change in the subcutaneous tissues. The lesions are extremely sensitive to pressure and sometimes cause good deal of pain.

Infection of the medulla of the hair shafts with *Trichophyton endothyx* produces what is known as 'black dot ringworm' of the scalp. The

lesions occur as multiple dry, scaly patches with the hair shafts broken off flush with the surface of the skin. The follicles are not affected at first but undergo sclerosis and atrophy late in the disease when the hair shafts are destroyed by the fungus. They produce complete alopecia.

The beard and moustache are sometimes attacked by the ectothryx variety of *Trichophyton (T. violaceum)* giving rise to pustular folliculitis and kerion.

TREATMENT. Local application of antiseptic lotions, paints and ointments are of little value. A cure can only be established by complete epilation of the infected hair shafts for which exposure to unfiltered X-rays is best. If there are suppurative lesions, calamine lotion, acriflavin lotion, or 5 per cent. solution of gentian violet in 20 per cent. alcohol should be used first. Sometimes kerion occurs owing to abnormal tissue reactions and this condition requires palliative treatment with starch poultices, carbolic or boric acid compress, as a preliminary to X-ray therapy. Careful prophylaxis is essential to prevent relapses, especially in boarding schools and dormitories. Weak antiseptic hair washes with perchloride of mercury, 1 in 2000, should be used once a week. Thallium acetate has been used orally to make the hair fall off, but owing to the toxic nature of this compound, its use is very risky.

Ringworms affecting the smooth skin. These belong to the genus *Epidermophyton* and give rise to eczema-like lesions which may be dry and scaly, or moist and inflamed, depending on the situation of the lesion as well as the friction of clothes, etc., producing maceration of the skin. In the moist areas, like the groin or axilla, the lesions are extremely irritable and vary in colour a good deal, the margin is usually squamous, sometimes vesico-pustular and weeping. This is popularly called *Dhobie's itch* and may sometimes spread over the entire surface of the body, palms, soles, nail and even the hair of the scalp. It is very resistant to treatment and relapses occur almost every rainy season. The diagnosis is not difficult in uncomplicated cases, but when there is secondary infection with pyogenic organisms, the true nature of the lesion may be overlooked. Definite diagnosis in straightforward cases or of a single patch can be made by scraping off the dry scales from the margin and examining under the microscope with suitable stains or other reagents, when the segmented mycelia of the *Epidermophyton* can be seen.

TREATMENT in such cases is fairly simple, and painting the affected area with tincture of iodine for three or four days usually effects a cure. Sulphur-camphor dusting powder sprinkled lightly on moist areas after bath is a very good and reliable prophylactic agent.

In chronic cases, various complications require special treatment which, in the beginning, has to be mainly symptomatic. The eczematous weeping areas should first be fomented thoroughly with weak lysol lotion (15 min. to 1 pint) at about 104°F. and kept moist with calamine

or other soothing lotions during the day. The intractable irritation often yields to salving with camphor and coconut oil (5 to 10 gr. to 1 oz.). The coconut oil itself possesses a certain amount of fungistatic properties. When the eczematous condition is better, specific treatment with resorcin, salicylic acid, benzoic acid, etc., can be commenced either as ointments or suspended in traumaticin.

The following prescriptions offer a good combination of remedial drugs which have been tested at the School of Tropical Medicine, Calcutta, and found efficacious :—

(1) Modified Whitfield's ointment. Salicylic acid 15 gr., benzoic acid 15 gr., vaseline 1 oz. Modifications with carbolic acid 3 gr. to 1 oz. or resorcin 10 gr. to 1 oz. are also of value.

(2) Resorcin $\frac{1}{2}$ dr., tincture benzoin compound 1 oz. painted once at night and removed with spirits the next day. This is useful in dry squamous ringworms, 3 to 4 days' treatment effecting a cure.

(3) Chrysarobin 5 to 10 gr., gutta percha 1 dr., chloroform 1 oz., to be dispensed in air-tight glass stoppered bottles, and painted on with small brush. This is also useful for dry types, one application sufficing.

(4) Cignolin (chrysarobin derivative) 1 to 3 gr., acetone pure 1 oz. This is also to be kept in air-tight glass stoppered bottle and painted with a fine brush. One application usually cures

In using chrysarobin and its derivatives great care should be taken to guard against inflammatory reactions, especially if the patient is a hypersensitive subject.

Chronic irritation sometimes produces hypertrophy of the deeper layers of the epidermis which is responsible for persistence of the itching even after the ringworm is cured. Such cases require adequate thyroid medication and keratolytic ointments like salicylic acid in fairly large doses— $\frac{1}{2}$ to 1 dr. to an ounce in lanolin base.

On the hard skin of the palms or soles this disease is very often associated with allergic states—*cheiropompholyx*, a condition which does not yield to vigorous and systematic local treatment. Under such conditions the cause of the allergy should be carefully investigated and removed, and then the local treatment will take effect.

In people who sweat rather profusely on their feet, a nidus of ringworm infection can almost always be found in the cleft between the fourth and fifth toes; the skin looks sodden and dead and starts itching as soon as it gets dry. Breach of surface epithelium favours secondary infection with pyogenic cocci, and inflammatory reactions and cellulitis are not uncommon complications which require special treatment as the merit of the cases demands. Uncomplicated cases are best treated mainly on prophylactic lines; the clefts between toes should be dried carefully after the bath and sprinkled lightly with sulphur-camphor dusting powder before putting on socks or stockings. Oozing of serum should be treated with 20 per cent. silver nitrate solution painted on at night

and repeated for four consecutive nights. Painting with resorcin $\frac{1}{2}$ dr. in an ounce of compound benzoin tincture for the subsequent 3 or 4 days effects a complete cure.

All other types of dry scaly ringworms of the body can be treated on these general lines and the importance of prophylaxis should be impressed upon the patient (1) Camphor and coconut oil (5 to 10 gr. to 1 oz.) to be rubbed well in before bath. (2) Lysol fomentation (15 to 20 drops to a pint of warm water) for naturally moist areas like the groin, scrotum and axilla, night and morning. (3) Ointments containing salicylic acid, resorcin and benzoic acid, applied twice daily. (4) Sulphur-camphor dusting powder when the irritative lesions are cured.

Ringworm of the nails. Two clinical varieties are commonly met with, namely, (a) *The hypertrophic form*: where the fungi affect the bed of the nail causing thickening and black discolouration of the matrix, which becomes very dry and brittle. The lesions can sometimes be seen as parallel lines along the long axes of the nails, and this gives it an appearance of 'worm-eaten wood'; the cuticle generally remains unaffected. Secondary infection may occur giving rise to paronychia when the soft tissues of the terminal phalanges become swollen and very painful so that hot fomentations, antiseptic baths or even surgical interference become necessary. Even the uncomplicated cases are difficult to treat owing to the fact that fresh nails growing on the beds at once become infected, and unless the whole nail is removed and the bed treated thoroughly, radical cure is not effected. Best results are however obtained by scraping the nail thin with a nail file or knife after softening with 5 per cent. solution of caustic soda and then painting with either 3 per cent. solution of copper sulphate or a paint consisting of perchloride of mercury 2 gr., tincture of iodine 1 dr., chrysarobin 10 gr., water 1 oz. It stains the nails rather badly. The scrapings should be done every day for about 6 months, which is the time taken by the nail to grow from the cuticle to the tip. Care should be taken not to injure the cuticle or any part of the soft tissues around the nails when scraping, otherwise the ringworm paint may produce intense irritation, or even drug dermatitis. For rapid shedding of the nail X-rays may be used, but certainly not as a routine measure. Prophylaxis is very important—especially for infection of toe nails; socks and stockings should be boiled every day, and the insole of shoes and slippers wiped with lysol lotion (1 in 20) every other day. Sulphur-camphor dusting powder should be used on the feet lightly sprinkled on the toes and between clefts before putting on socks or stockings.

• (b) *The atrophic form*: the fungus attacks the surface of the nail matrix which becomes very thin, friable and discolored. Growth of the nail is markedly hindered, and the cuticle at the base of the nail is sometimes raised up owing to the accumulation of dead keratin substances underneath. The horny skin tissues around the nails are some-

times infected especially in the toes. Treatment in such cases is not very difficult because all local applications can reach the site of infection which is more superficial than in the hypertrophic form. The same line of treatment and prophylaxis applies for both the hypertrophic and atrophic forms and it is necessary to continue with remedial measures for about 6 months.

Infection with Organisms of the Genus *Malassezia*. Two types of infection are met with:—(1) In the scalp, dry or oily type of seborrhœa, caused by *Malassezia ovalis*. (2) On the face, neck and body, fine furfuraceous, scaly, pigmented or depigmented lesions caused by *Malassezia furfur* and known as pityriasis versicolor or 'chuli'. It is not yet definitely known whether *Malassezia ovale* and *Malassezia furfur* are different species of the genus *Malassezia* or are the same organism undergoing morphological and cultural changes owing to difference in the substrate in which they are growing.

SEBORRHŒA. It is a mild inflammatory condition of the scalp and body due to infection by the fungus *Malassezia ovalis* or bottle bacillus of Unna. The primary infection is always on the scalp and later on, spreads on the face and the upper part of back and chest. On the face it causes acne and on the body, seborrhœic dermatitis. The predisposing factors are individual susceptibility and heredity, of which the latter determines the numerical distribution of the sebaceous glands in a particular area of the skin. The clinical character of the disease varies with the age. In infants, the 'vernix caseosa' becomes infected with bottle bacilli and forms what is called the 'milk crust' which produces irritation, inflammation and desquamation of the surface epithelium. A few weeks or months later, the clinical picture may be completely changed to one of infantile eczema owing to an acquired hypersensitiveness, generally to milk, which renders the skin very irritable, and this allergic state augments the inflammatory changes induced by the primary fungous infection. The lesions are mostly confined to the scalp, cheeks and legs, but may spread all over the body. As an acute or subacute condition, it produces severe irritation and scratching; the resulting breach of surface favours secondary infection with streptococci and staphylococci causing impetigo and boils.

TREATMENT. Remove the vernix caseosa by soaking well with olive oil and then apply mild soothing liniment, such as liniment calamine. For the impetigo, ammoniated mercury ointment 5 gr. to an ounce, or an ointment containing zinc oxide 10 gr., ammoniated mercury 2 gr., in one ounce of vaseline are used.

The disease usually remains quiescent between 5 and 15 years and reappears at puberty. In the scalp the dry type of seborrhœa is called dandruff or scurf and in subjects with hyperactive sebaceous glands, it produces seborrhœa oleosa. The scalp is full of white or greyish scales which may be dry and powdery in the dry type, or wet and clay like in

the oily type. The scales are formed by rapid desquamation of the horny layer consequent on the inflammation set up by the fungus. The degree and extent of the disease varies a good deal. On removing the scales red and inflamed areas are left on the scalp. The lesions may spread to the adjacent areas on the forehead, face, neck; the back of the ears is also a very common site of affection. In the early stages of the disease the mild irritation stimulates the growth of the hair but later on causes loss of hair and baldness.

TREATMENT. Remove the scales by soaking well with olive oil for one or two hours; shampoo the hair with spirit soap consisting of soft soap 1 oz., rectified spirit 2 oz., or green soap 1 oz., ether 1 oz., rectified spirit 1 oz., and then apply resorcin lotion containing resorcin—30 to 40 gr., spirit of ether 1 dr., spirit of rosemary 1 dr., castor oil 10 min., rose water up to 1 oz. For people with light coloured or grey hair, euresol should be substituted to avoid staining of the hair. If the disease does not yield to this treatment, apply an ointment containing acid salicylic 10 to 15 gr., sulphur precipitate $\frac{1}{2}$ oz., lanoline 2 dr., vaseline up to 1 oz. or mercury oleate ointment (10 per cent.) at night. In the morning remove the ointment with olive oil and apply the resorcin lotion after bath. Seborrhœa of the scalp is very persistent and requires prolonged treatment. When the acute conditions have subsided the application of the ointment at night is discontinued; the spirit soap shampoo is given twice weekly and the resorcin lotion is used as hair dressing every day. In severe cases the hair should be cropped short.

SEBORRHŒA CORPORIS. When the infection of the fungus spreads to the body, a mild inflammatory reaction of the skin of the neck and upper part of the trunk—commonly called flannel rash—is induced. The skin is covered with fine furfuraceous scales. Later on the skin may be thickened and lichenoid, the hair follicles may also be affected causing peri-follicular hyperkeratosis—seborrhœic folliculitis. On the face the follicles stand out prominently and are hard and shotty to the feel. Extension may occur to the trunk and extensor surfaces of the arms and forearms, and sometimes the whole body as far down as the lower extremities may be involved. The condition is very distressing when a large area is affected; it causes great irritation and the patient is seen scratching almost all the time.

Treatment. Sulphur is the sheet anchor of treatment in this disease. Any of the sulphur lotions, of which the following are used more commonly, can be applied after bath. *Yellow sulphur lotion* consists of precipitated sulphur 30 gr., glycerine 10 min., absolute alcohol 2 dr., lime water 2 dr., and water 1 oz. The *compound sulphur lotion* consists of precipitated sulphur 1 dr., rectified spirit 2 dr., salicylic acid 10 gr., tragacanth powder 5 gr., and water 1 oz. The sulphur lotion should be rubbed well on the affected area which is then dusted with a powder

containing precipitated sulphur 1 dr., camphor $\frac{1}{2}$ dr., acid benzoic 2 dr., starch powder $5\frac{1}{2}$ dr. When rapid desquamation is required *white sulphur lotion* consisting of sulphuretted potash 15 gr., zinc sulphate 15 gr., tragacanth powder 4 gr., water 1 oz. can be used.

ACNE VULGARIS. It is an inflammatory condition of the sebaceous glands caused by *Malassezia ovalis*. The predisposing causes are, (i) age—it occurs during puberty when the sebaceous glands undergo full and rapid development along with the attainment of functional maturity of the gonads, (ii) constitutional disorder, e.g., anæmia, (iii) constipation and (iv) too highly fatty food or excess of carbohydrate in the diet. The determining cause is infection by the fungus and the contributory cause, a secondary staphylococcal infection leading to suppuration. The excessive secretion of the sebaceous glands favours the growth of the fungus which obstructs the gland mouths and thereby sets up local irritation. The plug obstructing the mouth of the glands is called the comedo and consists of the desquamated horny epithelial cells and a mass of fungi. The obstruction causes a condition of partial anærobiasis which favours the growth of the acne bacillus. The commonest sites of this affection are the face and forehead, but the upper part of the back and front of the chest are also affected.

Treatment. (i) General. Correction of constipation, dyspepsia or anæmia and improvement of the general health are very important. Diet should be light and easily digestible. (ii) Seborrhœa should be effectively treated. (iii) Local. The comedones should be pressed out with an extractor and not by means of the finger nails. The face should be washed in hot water—as hot as the patient can bear—and sulphur or spirit soap, and then one of the sulphur lotions applied locally. When suppuration has taken place, the boils should be lanced and antiseptic compresses applied. Staphylococcal vaccines are sometimes useful in suppurative cases. In severe and intractable cases X-rays improve the condition.

PITYRIASIS VERSICOLOR. (Bengali—*Chull*). The lesions, in this condition consist of yellow or yellowish brown, slightly scaly, macular patches, mostly on the trunk, face, neck and sometimes on the upper extremities. As a rule it does not extend to lower extremities. Except for causing discolouration of the skin and slight itching it does not produce any subjective symptoms. The disease is commonly seen during summer and the rainy seasons.

Treatment. Hot bath with sulphur soap for toilet and then application of one of the sulphur lotions. The sulphur-camphor dusting powder should be used as a prophylactic for some time after the cure is effected and in the beginning of every summer and rainy seasons.

It should be explained to the patient that the nidus of infection is in the roots of hair and regular treatment of the scalp with shampoo and resorcin or eucresol hair lotion is essential. Mustard oil has a

certain amount of inhibitory action on *Malassczia ovale* and can be used with advantage. European patients, however, do not like the greasy feel in the hair. Beta naphthol 20 gr., dissolved in an ounce of cocoanut or olive oil can be used for soaking into hair overnight which can be washed off with spirit soap shampoo the next morning. For extensive cases involving the face and body, separate towels for drying the head, and the face and body is recommended. Swabbing the forehead, back of the neck, ears, axillæ and groins with rectified spirit every day after bath prevents spread of the infection on the body.

ACTINOMYCOTIC LESIONS OF THE SKIN AND NAILS. The causative organism, *Actinomyces keratolytica*, affects the horny skin of the soles of feet, the nail beds in the toes and the hard skin at the bases of the balls of the toes. Clinically, three types of lesions are met with, viz., 'haja' or sodden skin, 'phata' or cracked foot and 'chaluni' or sieve-like condition of the soles. The toe nails, when affected, appear thinned out 'worm eaten' and almost black in colour. The palms of the hands are affected in a small percentage of cases. In all cases there is an associated hypertrophy of the horny layer with areas of keratolysis distributed in lines—'phata'—or around small circumscribed pits—'chaluni'—going as deep as the true skin and which makes walking extremely painful. Secondary infection and abscesses are not uncommon complications from mechanical injury from thorns or gravel.

Treatment. Treatment consists of cleansing up the cracks and pits thoroughly and painting with commercial formalin lotion (15 to 30 min. to 1 oz. of water or glycerin). Prophylaxis in the way of protection with shoes or sandals is very important.

External Diseases due to Bacteria

STAPHYLOCOCCI. Infection of the skin by these organisms may be divided into three main groups : (a) superficial infection of the hair follicles causing suppurative folliculitis (sycosis); (b) infection of the sebaceous glands and the adjacent tissues causing a certain amount of tissue necrosis and formation of limiting barriers—boils and abscesses; (c) infection of deeper structures, such as sebaceous glands and sweat glands, with extensive tissue necrosis and tendency to rapid extension—carbuncles. Staphylococci are universally present on cutaneous and mucous surfaces which are in contact or in communication with the external air. So long as there is no breach of surface from external injuries, chemical or mechanical, staphylococci can be harboured for an indefinite period without causing any lesions. The organisms can sometimes gain entrance into the deeper structures by lymphatic permeation. The most important portals of entry are the dilated mouths of sebaceous, sweat or mucous glands, even though the surface of the skin or mucous membrane may remain intact. Depending on the vitality of the tissues invaded and the toxicity of the strain

of staphylococcus, there may be produced simple boils involving only the hair follicles, abscesses with a certain amount of necrosis of tissues and formation of limiting barriers to the inflammatory process or carbuncles with extensive sloughing of the tissues tending to spread fairly rapidly in all directions. The primary lesions are not very difficult to diagnose and in all the lesions, whether superficial or deep, the four important signs and symptoms are always present, namely, pain, heat, redness and swelling.

Superficial infection. The hair follicles of the moustache and beard areas, front part of the legs, front and outer sides of the thighs, and the pubic region are sometimes infected by staphylococci giving rise to a condition called sycosis (barber's itch or coccogenic folliculitis). Each hair shaft is surrounded by an inflammatory pustule, the follicles are distended, painful and irritable, the skin between affected follicles being erythematous and painful. There is always a tendency towards cicatrization on healing so that the hair is completely destroyed and the skin badly scarred. In men, it is a particularly intractable disease in the shaving area and usually cure is prevented by infection of fresh follicles by the razor blade. In India, friction of the border of the 'dhoti' or 'sari' keeps up the disease in the shin areas. In rare instances, all the follicles of the body hairs, including those of the eyebrows and eyelashes, may be affected.

Treatment. Patients should be advised to give up shaving for sometime. The skin should be cleansed with warm olive oil and gentle friction with a piece of soft muslin or gauze followed by swabbing with weak antiseptic lotion, e.g., 1 per cent. carbolic lotion. Hot boric compress is useful in cases with acute inflammatory reaction in markedly hirsute subjects. Manual epilation of all loosened hairs should be done morning and night. A very useful and reliable remedy is 5 per cent. gentian violet lotion in 20 per cent. alcohol,—(gentian violet 20 gr., absolute alcohol 1½ dr. and water 1 oz.)—painted on morning and night. The only objection is the staining of the skin which is rather difficult to wash off. Other aniline dyes have been tried with fairly good results but the same objection holds for all the remedies in this group. Vaccine therapy yields very indifferent results. Successful epilation of the affected area definitely establishes a cure, for which X-rays have been very effective. It is not advisable to expose large areas over a long period as it may produce X-ray dermatitis or burns.

Prophylaxis has to be carried out by the patient with meticulous care. The razor blade should be washed thoroughly with soap and water and wiped down with 20 per cent. formalin solution immediately after shaving; the brush should be kept soaking in 20 per cent. formalin lotion for half an hour and washed thoroughly in water immediately before use. All cuts and abrasions during shaving are to be touched with absolute alcohol which can also be used for swabbing the beard and moustache area after the shave. If the skin feels too harsh and irritable,

salving with liquid paraffin at night has a very soothing effect and ensures an easier shave the next morning. Too frequent washing with soap and water is decidedly harmful.

BOILS AND CARBUNCLES. In the initial stage when the boil is just coming up, the best treatment is to apply cold compresses to reduce the hyperæmia and relieve the tension on the soft tissues. Weak antiseptic lotions, e.g., acriflavin 1 in 5000, carbolic acid 1 in 100, or plain calamine lotion can be used with advantage, and this line of treatment may abort the formation of a boil or an abscess in a certain percentage of cases. Exposure to ultraviolet light is very beneficial at this stage and sometimes prevents formation of the abscess. There should be no surgical interference unless and until pus has formed and the abscess is walled off from the surrounding tissues by a barrier of granulation tissue. After lancing, a hot compress, changed every 4 hours, is recommended to dislodge the adherent slough. The hot compress sometimes infects fresh sebaceous gland mouths in hairy areas like the axilla or pubis. The surrounding skin should be well swabbed with absolute alcohol morning and night with a view to sterilizing and hardening the skin, thus making it more resistant to infection. When the cavity is nearly filled up, it should be dressed with borovaseline ointment. Staphylococcal vaccine is not of any great curative value but it is a good prophylactic for people susceptible to 'mango boils' which recur with almost unvarying regularity every summer and rainy season. Usually, such people are subject to active seborrhœa of the scalp and treatment should be directed towards this important focus in order to prevent relapses. Recurrences and resistance to treatment are, in a small percentage of cases, due to lowered defensive power of the tissues—local kataphylaxia; such cases require internal administration of calcium, manganese or tin salts to restore normal tissue metabolism. Prophylaxis is adopted on the same lines as for seborrhœa. For carbuncles, hot boric compress and exposure to ultraviolet light are useful in the initial stage. When there is marked œdema of tissues or extensive sloughing, the affected area should be incised and dressed aseptically. Vaccines are useful at this stage and local packing with gauze soaked in antiviral lotions are effective.

Staphylococcal infection of the deeper tissues sometimes produces granulomatous nodules growing above and out of the general skin surface. The condition is called *granuloma pyogenicum* or *botryomycosis*.

PRICKLY HEAT. The affection begins in people who sweat rather profusely during summer months in the tropics and are in the habit of wearing too many tight-fitting clothes. The mouths of the sweat glands are obstructed owing to a sodden condition of the epithelium due to excessive perspiration and this produces sudamina vesicles on the body and desquamation on the palms. These sudamina are tiny

vesicles filled with clear fluid, the lesions being mostly found in the axillæ, bends of the elbows, on the chest, and in children usually on the back. Individual lesions are surrounded by a red inflammatory areola and are called prickly heat. They are extremely irritable and when abraded may develop into pustules which eventually lead to the formation of boils and abscesses. When these vesicles are infected secondarily with staphylococci, they appear white, like sago grains. In the axillæ these pustules generally attain fairly large size and are called *Pyosis mansonii*. Persons subject to seborrhœa are more susceptible to prickly heat because the primary infection with the fungus causes obstruction of the mouths of the sweat glands and consequent irritation favours secondary infection with staphylococci.

Treatment. The most important measures to check this excessive sweating are curtailment of vigorous physical exertions, avoidance of heavy tight-fitting clothes and hot, spiced foods. Intense irritation is best controlled by swabbing with calamine lotion or ammonia solution (1 dr. of Scrubb's ammonia to a pint of cold water) and sprinkling with sulphur-camphor dusting powder. Talcum powder is recommended for sensitive skins because they tend to develop sulphur dermatitis. The scalp must be treated with resorcin lotion at the same time as otherwise the local treatment of the skin will only give temporary relief. *Prophylaxis.* The precautionary measures should be commenced before the humid pre-monsoon season has set in and carried on until the rainy season is almost over.

STREPTOCOCCI. Streptococcal infection of the skin is superficial in character and produces a good deal of induration of the tissues with accompanying lymphangitis and a certain amount of constitutional disturbance. These organisms are present in healthy tonsils, teeth, intestines and other mucus surfaces but are hardly ever found on the surface of the skin. The extent of damage to the tissues depends, as in the case of staphylococci, on the susceptibility of the patient and toxicity of the infective strain. Streptococcal infection of the skin may be divided into (a) acute infection of the skin spreading rapidly through the lymphatics—*erysipelas*, (b) sub-acute superficial infection—*impetigo contagiosa*, and (c) chronic infection which is mostly localised—*ecthyma*.

ERYSIPELAS. The skin and subcutaneous tissues are acutely inflamed and there is induration of the deeper tissues. Clinically, the appearance varies from a transient hyperæmia to intense inflammation, vesiculation or even sloughing. There is localised swelling, redness and heat, the border is raised, brawny and indurated and the infection advances rapidly along the lymphatics. The centre of the lesion is paler than the margin and here the skin shows early degeneration. The onset is generally preceded by malaise and depression and is accompanied by severe constitutional symptoms. The fever which is often

preceded by a fairly prolonged rigor may rise as high as 105°C. All the symptoms of severe intoxication, namely headache, vomiting, anorexia, and joint pains are present; there is marked leucocytosis. In the worst types of cases, bronchopneumonia, hæmaturia, cutaneous petechiae, septic embolism or meningitis may supervene within two or three days of the onset. Such cases end fatally, especially in the two extremes of life. Cases of moderate severity, however, run an acute course lasting for about a week or 10 days after which the cutaneous inflammatory reaction subsides, the advance is arrested, the temperature comes down by lysis and general toxic symptoms gradually clear up. The affected area may remain hyperæsthetic for a considerable time after cure and show impaired capillary circulation, alopecia, thrombo-phlebitis or telangiectasis. Recurrent types of erysipelas have been described which are consequent on an active septic focus in the bowels, teeth, tonsils or throat and nose; the clinical picture is that of an acute lymphangitis and lymphœdema with access of fairly high temperature preceded by rigor. The duration is short, lasting about 3 to 5 days, and constitutional disturbances and toxæmia are not very severe. Any part of the body may be affected and repeated attacks at the same place result in a good deal of thickening of the subcutaneous tissues—a condition commonly known as *elephantiasis nostras*. The first attack is usually the most severe. Erysipelas of the facial area consequent on scratching an acne lesion is not only fairly common but is often fatal, especially in diabetic subjects.

Treatment. Palliative treatment is given during the acute stage. The patient should be strictly confined to bed with an ice cap if the temperature is above 102.4°F. Diuresis should be encouraged by frequent iced drinks; ice should be given to suck to control vomiting. Bowels should be opened with small enemata; rectal saline with glucose may be given if persistent vomiting interferes with the intake of nourishment. Alkaline mixtures are useful in so far as they help elimination to a great extent. Tinct. perchloride of iron in 15 min. doses can be given with advantage when the irritability of the stomach has abated. Liquid diet, e.g., barley water, gruel, diluted milk (if tolerated), glucose, raisin, tea, etc., should be given in small quantities and at frequent intervals; feeds should be iced to guard against recurrence of vomiting. *Local.* Iced compress of weak antiseptic lotions, e.g., acriflavin (1 in 5000) or boric acid 5 per cent. are very useful; lotio ichthyl 10 per cent. has also been found useful. The inflamed skin should be dusted with talcum powder and the area just beyond and all around the advancing edge painted thickly with surgeon's collodion or tincture perchloride of iron. All vesicles and pustules are carefully punctured with strict aseptic precautions and covered with dry dressings; surgical interference is necessary only when an abscess has formed. When the acute stage has subsided the parts should be dressed with 25 per cent. ichthyl ointment. *Specific.* Opinion is still divided on the use of anti-toxin or antiserum. Streptococci have very little of exotoxin and hence

it is believed that specific antisera are of hardly any curative value. Recently, polyvalent antistreptococcal specific sera have been produced by firms of repute and the results of treatment with these sera are very encouraging. Twenty c.cm. of the serum should be given subcutaneously as early in the disease as possible, all precautions being duly taken to guard against anaphylaxis in sensitive subjects. Injections are given every other day, the total quantity required to effect a cure hardly exceeds 150 c.cm. Calcium lactate 15 gr. is given per os three times a day during the course of injections. Oral administration of serum is of very doubtful efficacy. In children blood transfusion has good effects. *Curative and prophylactic.* To prevent recurrences a thorough investigation should be made to locate any latent septic focus or any other latent concurrent disease. With this object in view the clinician should combine with the laboratory worker so that both may work hand in hand for the benefit of the patient. It should be borne in mind that a single negative laboratory finding is of no significance at all; it is only after careful repeated examinations that one can definitely affirm or deny the presence of latent septic foci. Autogenous vaccines are of great value in this particular field. General tonics, e.g., iron, arsenic, calcium, and nourishing food and change to a salubrious climate constitute the three important adjuncts on which cure and prophylaxis are based.

IMPETIGO CONTAGIOSA. The commonest superficial lesion of the skin due to streptococci is *impetigo contagiosa* which is characterised by shallow ulcers surrounded by a halo of light erythema—(only seen in fair subjects) and covered with a light yellowish crust. There is slight oozing of serum which is charged with streptococci. The disease is auto-inoculable and contagious to others. The patient usually inoculates himself over various places from the exudate by unconscious picking and scratching and in schools and boarding houses it may occasionally spread in epidemic form. Children are more susceptible than adults owing to the skin being very fine in texture and it is a common experience to find babies in arms picking up the infection from other children or even their ayahs and nurses and then passing it on to the mother. The ulcers involve only the superficial layers of the epidermis and do not leave any scar on healing. As a rule they are not very painful but somewhat tender on pressure. There is always a certain amount of hyperpigmentation at the periphery of the healed area, but this gradually fades out provided the lesions are not of very long standing.

Treatment. Ammoniated mercury, 5 to 10 gr. to an ounce of lanoline or vaseline base, acts as a specific. Cure is established in 3 to 5 days. The superficial crusts should be softened with olive oil and gently removed before a thin smear of the ointment is applied night and morning. Induration and weeping which accompany some cases are best controlled with cold compresses of weak acriflavin lotion (1 in 3 to

5 thousands) or continuous application of calamine lotion. Repeated attacks at the same site produce tissue kataphylaxia, which condition requires general treatment with iron and arsenic tonics or cod liver oil. Vaccine therapy is hardly ever necessary except in long standing cases in adults where lowered vitality retards healing. The deep or veldt sore type of impetigo which is often found on the hands and feet does not respond to treatment with ammoniated mercury; the lesions are deeper, crateriform with good deal of sanious discharge and are often confused with Naga sore. Cold compresses with 1 in 3,000 acriflavin lotion clear up the lesions in about a week or 10 days. Auto-vaccine is of proved curative value.

ECTHYMA. This condition is very similar to impetigo but the infection extends more deeply in the skin and involves the corium. It usually begins as a vesicle or vesico-pustule which enlarges fairly rapidly and ulcerates with formation of a thick crust adherent at its edges to the skin. Lesions are usually multiple and in some instances are ushered in with fever and malaise. There may be a good deal of pain and tenderness owing to its deeper situation and the induration of the tissues. When the crust is removed a saucer-shaped ulcer with a raw base and elevated edges is revealed. These ulcers are auto-inoculable and leave pigmented or depigmented scars on healing.

Treatment. The crusts should be removed by soaking with warm olive oil, no soap and water should be used subsequently. Locally, cold compress with 1 in 3000 acriflavin lotion during the day, weak ammoniated mercury ointment (5 gr. to 1 oz.) or borovaseline at night yield the best results. In extensive cases the patient should be kept in bed and treated with iron and arsenic tonics or calcium lactate 10 gr. and parathyroid 1/10 gr. twice daily on an empty stomach. Every attention should be paid to improve the general health especially in growing children who respond well to cod-liver oil, malt or ostelin. Sunlight and ultra-violet radiation are valuable adjuvants in delicate subjects. Autogenous vaccine is of proved curative value but disappointing results are inevitable if too much faith is pinned on the injections alone. All focal infections should be carefully sought for and treated thoroughly.

DIPHTHERIA. Infection of the skin by *Corynebacterium diphtheriae* occurs as an acute primary condition or as a secondary infection on pre-existing sores and abrasion of the skin. The cutaneous involvement may be independent of infection of the mucous membranes. The characteristic lesions shew ulcers with swollen edges and a false membrane of a greyish colour covering the base. Constitutional symptoms are fairly severe and out of proportion to the number of ulcers which are rarely multiple especially in the primary type of cases. The disease is highly contagious and usually more than one inmate is affected in boarding schools or army barracks. Impairment of the

cardiac function sets in early and the case often terminates fatally if specific treatment is delayed too long.

Treatment. Injection of the antitoxin in full doses (50,000 units) near the lesion gives uniformly successful results. Local dressing with lint soaked with the antitoxin is also indicated. The injections should be repeated till constitutional symptoms disappear. Segregation and quarantine are essential for preventing an epidemic in boarding schools, etc.

ANTHRAX (Malignant pustule). The disease is caused by a spore forming bacillus, *Bacillus anthracis*, and is commonly seen in people dealing in hides, cattle farmers, wool sorters, tanners, butchers and stable grooms. A few cases have been reported to have occurred from the use of cheap pony-hair shaving brushes. It is an acute and generally fatal disease with accompanying suppurative adenitis and grave constitutional symptoms, septicæmia and metastatic abscesses. A typical lesion is generally seen as an inflammatory papule within a few hours after the infection. The inflammation spreads rapidly and a blister appears surrounded by intense infiltration and oedema. Spontaneous rupture of the vesicle occurs early, exposing a dark brown eschar surrounded by small vesicles and pustules resting on a red, swollen and indurated base. The discharge is purulent or sanguineous and is full of *B. anthracis*. The inflammatory signs increase, oedema of the tissues spreads, other bullæ develop accompanied by high temperature and grave constitutional symptoms. The regional lymph glands suppurate, and septicæmia with metastatic abscesses in vital organs precipitate a fatal termination. In milder cases, the constitutional symptoms are slight and the gangrenous tissue sloughs out leaving a clean ulcer which heals by formation of granulation tissue.

Treatment. Immediate and wide excision is urgently indicated. When the face is involved multiple incisions and cauterising with phenol or tincture of iodine may be substituted for wide excision which causes marked disfigurement. Antianthrax serum should be given early with an initial dose of 100 c.cm. The dose is repeated till the fever subsides. Injection of the serum at the site of the lesion is recommended and sometimes yields good results. Normal bovine serum, which has a certain amount of antibodies against anthrax normally present may also be used when antianthrax serum is not available.

All linen, clothes and utensils should be sterilised every day in the autoclave at a temperature of 120°C. The soiled dressings should be burnt at once.

GLANDERS (Equinia, Farcy). The disease is caused by infection with *Actinobacillus mallei* and is commonly seen in grooms, veterinarians and cattlemen in either an acute or chronic form. The skin of the face and the nasal mucous membranes are commonly affected. A typical skin lesion begins as an inflamed papule or vesicle which

rapidly becomes nodular and then pustular and ulcerated. The ulcers are irregular, excavated with undermined edges and the base is covered with purulent or sanguineous discharge. In the course of a few days or weeks secondary nodules appear along the lymphatics; these break down and result in confluent sloughing, ulcerating lesions involving extensive areas of the skin. Infection of the nasal mucous membrane is characterised by a preliminary catarrh and epistaxis followed in a few days or weeks by extensive ulceration and sloughing with purulent discharge loaded with bacilli. In severe cases the temperature ranges high and a fatal termination is heralded by asthenic diarrhoea and involvement of the intestines. Constitutional symptoms are less severe in chronic cases but a fatal termination from intercurrent diseases, nephritis and general exhaustion is almost the rule.

Treatment. Immediate excision and curettage followed by cauterising with phenol is the most important measure to save the patient. Injection of the antitoxin, Mallein, in 1 to 2 c.cm. doses is of considerable value especially in chronic cases which have to be treated more or less symptomatically in other respects.

Segregation and precautions regarding sterilisation of linens, utensils, etc., is of great importance in prevention of the disease which, fortunately, has become quite rare nowadays.

Tuberculosis of the Skin

The lesions produced by *Mycobacterium tuberculosis* are either primary or secondary to pre-existing lesions due to various causes. Whatever be the character of infection, the reaction of the skin to invasion with tubercle bacilli varies widely in different subjects and hence the clinical appearance, course, duration and response to treatment of skin tuberculosis vary widely as well. The criterion of diagnosis is, in all cases, based upon the histological changes seen in biopsy material and upon the results of animal inoculation with emulsion of tissues removed from the affected areas. Evidence of tuberculous lesions elsewhere in the body and reaction to tuberculin are taken as corroborative of histological diagnosis. The lesions are clinically classified as follows:—*Localised forms*—(i) Lupus vulgaris, (ii) Ulcerative tuberculosis, (iii) Verrucose tuberculosis, (iv) Scrofuloderma. *Exanthematic forms*—(i) Miliary tuberculosis, (ii) Lichen scrofulosorum, (iii) Papulonecrotic type, (iv) Erythema induratum or Bazin's disease, (v) Sarcoid of Darier, Roussey and Boeck.

(A) LOCALISED FORMS. (i) *Lupus vulgaris*. The lesion consists of very small minute nodules, translucent in colour and deeply embedded in the infiltrated true skin, and thereby giving rise to reddish brown patches which heal in the centre with production of deep depigmented scars and spread diffusely at the other parts of the lesion for an indefinite period of time. On diascopic examination the active

portions of the lesion can be seen to be composed of deep-seated granulation tissue with characteristic 'apple-jelly' colour. Fairly large plaques are formed by coalescence and development of new nodules and these may be elevated above the level of the skin. Adherent scales are frequently seen especially at the margins. The disease causes wide destruction of the tissues and leads to very ugly deformities, contractures and ectropion. There are two clinical types of lupus vulgaris, namely, atrophic and hypertrophic; both types may set in acutely and in rare instances in more than one area at the same time with a fair amount of constitutional disturbances; this is especially noticed when there are active foci of systemic infection as well.

The face, particularly the nose, is most frequently affected although the lesions may appear on any part of the body including the mucous membranes.

In the atrophic type of the disease, the nodules undergo spontaneous involution and ultimately disappear, leaving thin, scaly, atrophic and depigmented scars. On the other hand, healing may not take place and the margins then assume a gyrate or serpiginous outline and continue to spread with formation of minute fresh nodules.

The hypertrophic form is characterised by hard, thick, rough and depigmented cicatrices which are almost like keloids. In the genital region, ankles and dorsum of the feet the lesions often become papillomatous or even verrucose in character with a fair amount of exudation and formation of crusts. Papillomatous types of lesion are also found on the mucous membranes of the nose and lips, the individual patches being sharply defined and of reddish or grayish colour. Lupus vulgaris like all other tuberculous diseases, is slowly progressive and its chronic course may extend over many years with periods of intermission and exacerbation.

(II) **Ulcerative type.** This disease is almost always secondary to active tuberculosis of the internal organs and attacks the contiguous skin of the mouth, nose, anus, urethra and vulva. During the early stages, small yellow miliary tubercles form on the skin and these break down in the course of a couple of weeks into oval or rounded granulating, sluggish and painless open ulcers. The lesions are comparatively superficial; the edges are soft and irregular and the bases are raw, uneven and sometimes purulent. Formation of thin yellowish crusts is not very rare. In rare instances, ulcerative tuberculosis may be superimposed on pre-existing lesions of the skin like simple injuries and impetigo. This type is always due to localised infection from outside, the site of predilection being the soles of the feet, backs of the hands, fingers and buttocks.

(III) **Verrucose type.** The lesion begins as a group of small wart like papules which increase in number and coalesce to form brownish or reddish coloured oval patches. There is a marked hypertrophy of the horny layer giving it a papillomatous appearance and the surface may

appear as if ploughed up and fissured. The margin of the patches is dark red and is accompanied with fair amount of exudation or even suppuration and crusting. Patches are usually single and occur on the exposed parts of the body following contact with infected materials especially tuberculous cadavers or carcasses. In children, the disease is often seen on the buttocks knees and thighs as they are in the habit of pulling themselves along the floor and thus come in contact with infected sputum. In people walking bare feet the disease is commonly seen on the soles. Sometimes vegetative outgrowths appear at the periphery where extension takes place by coalescence of contiguous patches. The disease runs a very chronic course; spontaneous recovery occasionally takes place leaving thin depigmented scars at the affected areas. *Verruca necrogenica* or post mortem wart is another type of verrucose tuberculous lesion and occurs on the dorsal surface of the thumb or fingers particularly on or near the knuckles and interphalangeal joints; they generally appear at the site of some previous injury or abrasion. The lesions consist of pea or bean sized papular, indurated, warty outgrowths which are red or whitish in colour, and always keratotic. Extension occurs by peripheral spread but they hardly ever break down into open ulcers. Sometimes they disappear spontaneously leaving practically no scars. *Verruca necrogenica* is very rarely followed or accompanied by generalised tuberculosis. Occasionally these warty lesions are infected secondarily by streptococci or staphylococci with ensuing erysipelas or septicæmia. The disease almost exclusively affects butchers, packing house employees, pathologists, anatomists and dissecting room attendants.

(iv) *Scrofuloderma*. The involvement of the skin is by direct extension of the tuberculous disease from glands and lymphatic nodes or subjacent bones. The lesions are in reality the mouths of sinuses leading to the primary caseating or suppurating primary lesion. There is almost continuous discharge of purulent matter from these sinuses the walls of which are reddish, granular and bleed easily. Extensive ulcers are formed when several superficial sinuses run into each other. The subjective symptoms are trivial and constitutional disturbances are very slight or entirely absent. The disease often persists for years and in a large number of cases spontaneous recovery takes place with formation of rough, thick cord-like cicatrices resembling a keloid. Over 80 per cent. of the patients are children and young adults.

Treatment. General hygienic measures are of great importance. The patient should have plenty of good nourishing food plainly but agreeably cooked. Fresh air, sun light and change to a suitable climate are strongly recommended. General irradiation with ultra-violet light for hours at a time has proved to be of definite value.

Internally, cod-liver oil when tolerated should be given in full doses. Preparations of vitamin D, e.g., Ostelin, Irradol, Radiostoleum, etc., are also of proved benefit. Hypophosphites and lactate of calcium

should be given in 10 gr. doses with the two principal meals. Liq. arsenic hydrochlor. in 2 to 5 min. doses is also useful as an alterative and general tonic. Tuberculin in graded doses yields good results in the non-ulcerative lupus vulgaris and tuberculosis verrucosa cutis; ulcerative types do not respond well to tuberculin. A few cases respond well to thyroid extract in one grain doses.

Locally, the best cosmetic results are obtained by heliotherapy with the Finsen lamp but the tediousness of the prolonged treatment is a serious drawback. For rapid improvement X-rays may be substituted but the resulting scars are very hard and disfiguring, especially in case of lupus vulgaris of the face. For smaller lesions of the non-ulcerative type removal by freezing with carbon dioxide snow is the best. Larger patches should be removed either by excision or by surgical diathermy, cutting widely outside the affected area, and deep enough to reach the muscles. Local packs containing 5 per cent. oleate of mercury and 5 per cent. salicylic acid are very useful for verrucose tuberculosis. Salicylic acid and creosote paste prepared by mixing equal parts of each has been used at the Calcutta School of Tropical Medicine with very good results. The paste is spread on a piece of lint and applied to the affected area and secured with a bandage. This is removed when the patient complains of a burning sensation which is felt after about 48 hours. The lesions usually heal up with two such applications; 2 to 5 per cent. pyrogallic acid ointment is also useful. The site is subsequently treated with soothing liniments and creams. Ektabin ointment prepared from detoxicated tubercle bacilli is beneficial in non-ulcerative types of lesions.

For tuberculous lesions on mucous membranes iodides are given internally in full doses and the patch is kept soaked in hydrogen peroxide in gauze pack. Cure is established by liberation of nascent iodide in the affected tissue. Sodium iodide ionisation is recommended in intranasal lupus vulgaris. The prognosis in tuberculosis of the skin is good as regards life but unfavourable as regards a permanent cure. Except for the verrucose type and lupus vulgaris, all the other types of local lesions are refractory to treatment and very often recur after an apparently complete recovery. Carcinomata may sometimes develop in old scars of lupus vulgaris.

(B) EXANTHERMATIC FORM. (4) *Miliary tuberculosis.* This rare form of skin tuberculosis is nearly always associated with systemic infection and is characterised by an acute generalised eruption of small brownish red papules which break down early and form indolent ulcers. These ulcers are shallow with a circular border which is of a dull reddish colour, the base is pale and uneven and studded with small nodules of miliary growth along with seropurulent discharge. The disease affects small children of strumous diathesis after attacks of measles, scarlet fever or early pulmonary tuberculosis or in adults with advanced pulmonary tuberculosis. Its appearance generally forebodes a fatal termi-

nation. Localised forms are sometimes seen affecting the skin over softening tuberculous glands. The bacilli reach the skin as minute emboli through the blood stream.

(ii) **Lichen scrofulosorum.** The lesions consist of groups of minute, keratotic, follicular papules of light reddish brown colour scattered over the trunk or extremities. Individual papules are firm, flat-topped and may be capped by a tiny pustule or thin scales. The disease is generally found in children with tuberculous affection of the bones or internal organs. It persists for years causing no subjective symptoms. Occasionally spontaneous recovery followed by recurrences are noticed.

(iii) **Papulonecrotic type** (also known as acnitis, folliclis, acne scrofulosorum) :—The lesions generally appear in successive crops on the extensor aspects of the extremities, face and trunk and are characterised by small, firm, discrete, follicular papules which undergo necrosis in the centre and heal spontaneously leaving deep pitted scars. Children and young adults with active systemic tuberculosis are usually affected. The lesions are roughly symmetrical and begin as papulovesicles which develop into nodules, break down and heal up in two to three months to be followed by fresh outbreaks. The papulonecrotic type of skin tuberculosis is often associated with other forms of tuberculous disease of the skin, particularly erythema induratum and scrofuloderma.

(iv) **Erythema induratum.** The disease is characterised by symmetrical, deep seated, indurated, nodular formations about the subcutaneous vessels of the lower legs and is almost exclusively found in young women with glandular tuberculosis. In their early stages, the lesions consist of tender erythematous indurations which slowly develop into deep-seated nodules, the overlying skin becomes dusky or bluish in the course of a couple of months. The centre of the nodules then begins to soften and ultimately breaks down into irregular deeply excavated ulcers with thick undermined edges. Contiguous and neighbouring lesions often coalesce to form large ulcers. Spontaneous recovery generally takes place with formation of deep depigmented scars but fresh indurated nodules develop while the older ones are undergoing involution and thus the disease may persist for years. Constitutional symptoms are slight or even absent. The cause of the disease is attributed to the toxin of *Mycobacterium tuberculosis* causing deep seated 'lymphatism' and inflammatory changes.

(v) **Sarcoid.** (i) *Sarcoid of Darier and Roussey.* The lesions are found on the extensor surfaces of the lower extremities and are characterised by painless, oval or rounded subcutaneous nodules which do not tend to break down or ulcerate. Development of these nodular formations is slow and after persisting for several months they undergo spontaneous involution. Like erythema induratum the disease almost exclusively affects young women who show a strong positive reaction to tuberculin.

(H) *Boeck's sarcoid*. The lesion consists of multiple nodular groups of superficial granulomatous infiltrations, firm and elastic to palpation but without any tendency to break down and ulcerate. The entire cutis is affected, the epidermis remaining almost normal. The surface is covered by a fine net-work of capillaries which is more apparent in the case of a fully developed sarcoid than in the early stages. Evolution is generally slow and the nodules may take months to attain a certain size. Spontaneous recovery generally takes place although it may be delayed as long as a couple of years or so. The face is the site of predilection but the other parts of the body may also be involved. The disease is essentially of a benign nature and causes no symptoms. Its relationship to tuberculosis is doubtful.

Treatment. In view of the fact that exanthematic types of cutaneous tuberculosis is almost always associated with active systemic infection, the importance of general hygienic and dietetic measures cannot be too strongly stressed. Fresh open air life, good nourishing food, sun baths or general ultraviolet irradiation are necessities in spite of the tendency of this group of diseases to spontaneous recovery. In the majority of instances treatment of the active systemic focus prevents recurrences and leads to a permanent cure. Cod-liver oil and preparations of vitamin D in full doses are recommended for every case irrespective of the clinical type of lesions and this may be combined with hypophosphite of calcium in 10 gr. doses three times a day. Preparations of gold sodium thiosulphate, *e.g.*, Sanocrysin, Krysolgan, Solganal A and B, etc., can be used intravenously or intramuscularly with great advantage.

Local treatment has to be varied according to the nature of the disease. Miliary tuberculosis is best treated with Ektabin ointment after swabbing out with weak hydrogen peroxide. A 0.5 per cent. ammoniated mercury ointment may also be used in place of Ektabin. Inunction with raw cod-liver oil has been recommended for lichen scrofulosorum but the objectionable fishy odour is far from pleasing to the patient. An emulsion of liquid paraffin containing 1 per cent. thymol and 3 per cent. of Goulard's extract often yields very good results. The papulonecrotic types of lesions are best treated on conservative lines with cold compresses of calamine or 1 in 5,000 acriflavin lotion. Scars may be softened by gentle massage with hydrous lanolin every night. For erythema induratum, rest and elevation of the affected limbs is the most important part of the treatment. In the preulcerative stage, pain and induration respond to continuous application of calamine and weak acriflavin lotions. When deep ulcers are formed, washing with normal or hypertonic saline followed by dry dressing with antiseptic dusting powders, *e.g.*, thymol iodide or aristol is recommended. An elastic cotton or crepe bandage is also very helpful. Indolent cases do well on circulatory stimulants like liq. strychnine

hydrochlor in 2 to 5 min. doses combined with injection of tuberculin in graduated doses and local ultra violet radiation.

TROPICAL ULCER OR NAGA SORE. The disease is characterised by single or multiple, round or oval ulcers on the exposed parts of the body, chiefly the legs, and occurs in epidemic form amongst indigent labourers in Terai areas during the damp humid monsoon months. The cases begin in May and increase during August, September and October and gradually fall in December. The lesions begin as small inflammatory papules which rapidly form into vesicles, rupture and progress into ulcers. Individual lesions vary somewhat in size and may be as large as 4 inches across; the edges are elevated, undermined and smooth or ragged with an inflamed halo around them; the base is depressed, granulomatous and sometimes covered with a false membrane. Satellite ulcers may develop by auto-inoculation near the original lesion or on other parts of the body. There is a thick, glairy, mucoid discharge which is sometimes sero-sanguineous. In the majority of instances the ulcers develop from some pre-existing minor wounds, the site of predilection being the anterior and posterior portions of the legs, dorsal parts of the feet and the ankles. Formation of crusts is occasionally seen. Some ulcers are extremely tender and painful while others are almost painless.

The disease is considered to be due to a Gram-positive diplococcus with secondary infection of fusiform bacilli and spirochaetes. It is probably transmitted to healthy subjects by some biting insect. Several members in the same family including children are affected by direct contact. A single attack does not confer immunity and the same individual may suffer every year with the advent of the rainy season.

Treatment. Best results are obtained when the patient can be kept at rest and a cold compress of hypertonic saline applied to the ulcers. Ambulatory cases respond well to a gauze pack soaked in a solution containing 10 to 15 per cent. phenol and 5 per cent. copper sulphate kept in place for 24 to 48 hours. Subsequently the wound is dressed with borovaseline or 1 per cent. ammoniated mercury ointment. Painting with a 3 per cent. solution of arsphenamine has been recommended but the results are unsatisfactory.

Prophylaxis in the way of protection from injuries is of great importance. It is also necessary to impress on the indigent labourers the necessity of personal hygiene and avoidance of overcrowding.

External Diseases due to Physical Causes

• **SUNLIGHT.** Extremes of heat and cold damage the skin by altering its normal blood supply through dilatation or constriction of the capillaries, arterioles and venules. In the tropics, the effects of heat of the sun are of importance particularly for European residents whose skin is naturally deficient in the protective filter, namely melanin

pigment. The actual damage, however, is caused more by the ultraviolet than the heat rays and hence erythema, sunburn and blistering of the skin is more intense at bathing beaches or in the open country where freedom from the dust and smoke, common to towns and cities, allows almost unimpaired action of the ultraviolet rays. The reaction varies a good deal according to the sensitiveness of the individual skin, blondes being more susceptible than brunettes. Subjective symptoms may appear within a few minutes of the exposure or may be delayed as long as the next day. The skin becomes intensely red and inflamed, there is a feeling of constant pain and burning, there may be actual vesication single or multiple, which in extreme cases, coalesce into a large bleb. When the reaction subsides, the skin is left more pigmented, and this gives a certain amount of protection against subsequent burns from exposure. In this way repeated exposures may induce sufficient pigmentation of the skin—'tanning of the skin'—to confer almost absolute immunity from solar dermatitis. Aged persons, however, react somewhat differently owing to the loss of elasticity of the skin and may develop keratoses and depigmented spots.

Treatment. Soothing creams, *e.g.*, rosewater ointment (U. S. P.) (spermaceti $\frac{1}{2}$ dr., white wax 3 dr., borax 15 gr., rosewater 5 dr. and liquid paraffin $\frac{1}{2}$ oz.) should be applied freely; the hyperæmic parts may be rubbed down with ice or the part is covered with a piece of lint or gauze wrung out of ice cold liquid paraffin and kept cold by gentle rubbing with ice.

Prophylaxis. Exposed parts should be smeared with a cream containing quinine hydrochloride (2 per cent.), bismuth oxycarbonate (5 per cent.) or disodium naphthol sulphate (5 per cent.) as these compounds absorb ultraviolet rays to a certain extent. They offer no protection against prolonged exposure. Black or red hats, veils and umbrellas offer good protection. Anointing the body with heavy vegetable oils is practiced by indigent people as protection.

DERMATITIS MEDICAMENTOSA. Local application of apparently harmless paints, plasters, liniments or ointments may set up most intensely acute dermatitis in some sensitive skins, the sequence of cause and effect being quite obvious both to the subject and the prescriber. The commonest drugs which cause acute dermatitis are of the nature of chemical irritants; the degree and intensity of the reaction varies according to the nature of vascular response of the skin to external stimuli. Hair dyes, lipsticks, nail paints, eyebrow pencils, depilatories and shaving creams have been active sources of acute dermatitis owing to the various chemicals incorporated therein. Some drugs taken internally also give rise to rashes. For detail see Drug Rashes.

Treatment. Discontinue the particular drug causing the irritation and apply cooling soothing lotions like liquid extract of hamamelis, cold cream or rosewater ointment. The affected parts should be

cleansed with olive oil or liquid paraffin, soap and water being avoided till the acute stage has passed off.

Prophylaxis. It is better to warn the patients to use all stimulating applications first on a small area of the affected part and watch its effects overnight. Extensive inflammation can thus be avoided.

DERMATITIS ARTEFACTA. These are self-inflicted injuries of varying degrees of depth and extent and are found only in highly neurotic subjects who use both chemical and physical means alike to cause the damage. The lesions are always in the accessible areas on the face, body, arms and legs and never on the back. They are quite bizarre both in shape and size and always trail off at one end. Treatment is extremely difficult especially in female patients who have to be kept under the most strictly careful watch. Psychoanalysis and mental therapy should be tried.

ERGO-DERMATOSES OR OCCUPATIONAL DERMATITIS. Various chemicals employed in industries cause a chronic eczematous condition of the skin amongst the workers. The initial damage to the protective horny layer of the skin is done by constant soaking of the hands in water. It has been found that even distilled water which is acid and hypotonic, produces desiccation of the epithelial cells. If it contains some inert salt in solution it may become concentrated and hypertonic from evaporation owing to body heat and lead to oedema of the cells. The dermatitis is thus induced on a hypersensitive or damaged skin so that the substances which the worker may have handled before without any ill-effects now cause intense inflammatory reaction. Repeated and prolonged contact with these products produce changes in the epidermis and vascularity of the skin and may sometimes lead to hyperplasia of the epithelium, keratosis and carcinoma. Barbers, washerwomen, workers in lime, paints and varnishes, photographers, bakers, jewellers, etc., all may develop occupational dermatitis and the diagnosis of this condition offers no great difficulty.

Treatment. In the acute stage symptomatic treatment is resorted to, the pain and irritation requiring suitable sedative local remedies more or less on the same lines as for acute inflammatory lesions due to other causes.

Prophylaxis. Whenever possible the source of irritation must be removed, but when it concerns the vital question of a man's bread and butter, it is difficult to ask him to give up his occupation. Ultraviolet radiation and intensive calcium therapy may prevent repeated extensive attacks.

Internal Diseases reflected on the Skin
DISEASES AFFECTING THE TEXTURE OF THE SKIN
AND ITS APPENDAGES

HYPERKERATOSIS OF THE HORNY LAYER, ICHTHYOSIS.

This disease, which is hereditary and familial, is characterised by the entire surface of the body being covered with dry, shiny scales, dirty grayish or brown in colour, harsh to the feel, and broken up into a 'harlequin' or 'fish scale' pattern by numerous furrows. This parchment-like condition is accompanied with loss of elasticity of the corium and defective development of the sebaceous and coil glands—*Ichthyosis neonatorum*. Lanugo hairs are absent and the scalp is completely bald in extreme cases, indicating involvement of the corium. Survival of such a child is of very short duration—*Ichthyosis gravis*. If the disease starts *in utero* still-birth is almost always the rule. The acquired disease usually appears within the first five years of life and is at first noticeable only during winter months, almost complete recovery occurring in summer. The skin is very harsh and dry, the horny layer has a shiny appearance and is traversed by numerous shallow cracks and ridges. There may be increased pigmentation, generalised or localised, owing to correlated depression of suprarenal function—*Ichthyosis nigra*. The distribution of the lesions is symmetrical with regular arborisations and formation of complex patterns. Local manifestations may be exaggerated into heaped up, pigmented, circumscribed, cornified excrescences on the skin—*Ichthyosis hystrix* (porcupine skin); or may appear as pigmented linear verrucose nævi—*Nævus unius lateris*—involving extensive areas of deeper tissues on the face, trunk or extremities. Onset of the disease is insidious and the progress generally slow without any marked improvement during summer months. The general health keeps fairly good although the subject remains very susceptible to slight variations in the atmospheric temperature. The mucous membranes are never involved.

HYPERKERATOSIS OF THE HAIR FOLLICLES; Keratosis follicularis. In this condition the horny epithelium surrounding the mouths of the hair follicles undergoes hypertrophy giving the skin a stippled or dotted appearance. The dots are usually small in size and are seen as solid horny plugs blocking the mouths of the hair follicles so that growth of hair is prevented. The stunted hair remains coiled up in the follicle and in some cases only the tip can be seen at the apex of the grayish keratotic cone. Each corneous plug may be surrounded by an erythematous halo and manual expression of these leaves minute shallow cup-shaped depressions which fill up again fairly rapidly. The unerupted hair may cause a good deal of irritation and the breach of surface produced by scratching may induce secondary pyogenic infection. The disease is most commonly found in xerodermic skin although normal skin may be similarly affected especially during winter.

LICHEN SPINULOSUS. It affects children mostly, the lesions being mildly inflammatory and consisting of minute grouped filiform spines protruding from the hair follicles. The elbows and knees are the sites of predilection although any part of the body may be affected. Spontaneous recovery takes place in a fairly large percentage of cases while others may shew recurrence at different sites every winter till the age of puberty.

Treatment. Local: The general principles adopted are first to soften the harsh dry scales with bland non-irritating oil followed by mild keratolytic ointments to induce exfoliation of scales and stimulate growth of healthy skin. The patient should be encouraged to anoint himself every day with olive oil or cocoanut oil which should be rubbed in with gentle massage and friction, preferably in the sun. He is then given a tepid alkaline bath for about 15 minutes, dried with a soft towel and salicylic acid ointment 30 gr. to 1 oz. of lanolin base is applied all over the affected area. Other keratolytic agents of stronger action are hardly required.

General: Good food, cod-liver oil and general hygienic measures are of importance. Bowel infection, protozoal, helminthic or bacterial, is often found in these cases and should be treated. Intensive thyroid medication cures a large percentage of cases and this is undertaken as follows. The patient is put to bed and kept at absolute rest for 12 hours and a mean count of his pulse rate is recorded. Next day he is given ext. thyroid sicc. $1/3$ to 1 gr. three times a day keeping a careful count of the morning and evening pulse rate. As soon as the pulse rate rises to 100 per minute, the thyroid extract is discontinued for 24 hours, by which time the pulse rate falls back to normal. Throughout the period of intensive medication the patient should on no account be allowed to sit up in bed even to relieve himself. The thyroid extract may then be continued in $\frac{1}{2}$ to 1 gr. doses twice daily for 2 weeks with the patient attending to his particular avocation. Cure is established in about six weeks provided the physiological functions of the thyroid gland of the patient are not already thrown permanently out of balance by other systemic diseases, e.g., syphilis. For infants and children intensive thyroid treatment is recommended with the same precautions about absolute rest as is the case of adults, a proportionate dose being given according to the age of the child. Lichen spinulosus and milder degrees of keratosis follicularis do not require intensive thyroid treatment, mild keratolytic ointments and paints generally establish a cure.

PITYRIASIS RUBRA PILARIS. A chronic hypertrophic disease of the epidermis characterised by hard yellow or pink papules of general or universal distribution and affecting chiefly the mouths of the sebaceous or sweat glands. Each lesion consists of a dry hard papule or a horny plug on the mouth of a sebaceous or sweat gland; they are at first discrete but tend to become confluent and involve extensive areas giving

rise to reddish, raised, thick, rough patches covered with brank-like scales. The sites of predilection are backs of the fingers especially of the first and second phalanges, backs of the hands, extensor surfaces of the arms, elbows, knees and the axillary folds. Deep fissures are sometimes formed at the joints. The skin of the face, palms and soles become thickened and inelastic and the nails hard, brittle and striated. Ectropion of the lower lids may occur. Lesions on the mucous membrane of the mouth are exceedingly rare. There are practically no subjective symptoms and the general health usually remains good. The aetiological factor is mainly a defective function of the thyroid gland together with parathyroid imbalance and defective calcium mobilisation in the system. Majority of the cases are seen amongst young adults, although children and old people are not exempt. Spontaneous recovery may take place but recurrences are common, even after two or three years of apparent freedom from the disease.

Treatment. *Local.* The skin should be well rubbed with olive oil or liquid paraffin for about half an hour before giving the patient an alkaline bath, after which a 10 per cent. salicylic acid ointment should be applied all over the affected areas. Carbolic carron oil is also very useful.

Internal. Intensive thyroid treatment followed by oral administration of thyroid $\frac{1}{4}$ gr., parathyroid $\frac{1}{10}$ gr., calcium lactate 10 gr., twice daily before food, establishes a cure.

SCLERODERMA. 'Hide-bound skin'. The condition is characterised by hyperkeratosis of the epidermis along with thickening and loss of elasticity of the skin owing to formation of bands of fibrous tissue in the corium. The distribution is usually regional although in extremely rare instances the whole body may be affected. Generalised types of cases are slowly progressive and almost always fatal. Strangulation of the cutaneous vessels by the constricting fibrous bands leads to extensive gangrene and sloughing of the skin; sometimes secondary pyogenic infection supervenes, followed by toxæmia. Complete loss of elasticity of the whole of the skin greatly impedes freedom of movement of the chest in respiration and death may occur from secondary asphyxia.

Localised scleroderma. It is characterised by occurrence of circumscribed or diffuse, hard, smooth, depigmented areas which are fairly adherent to the underlying soft tissues. There may or may not be any discolouration around these lesions. In the early stage of the onset the affected areas may be swollen and inflamed with excessive cornification but atrophy of the skin follows rapidly with formation of hard inelastic fibrous tissue in the corium. On the palms and soles the condition is known as *tylosis* in which flexion or extension of the fingers and toes become very limited in range. *Dupuytren's contraction* is probably scleroderma of the palmar fascia. Such bands of fibrous

tissue are sometimes formed at the tips of the terminal phalanges causing, at first, thickening of the skin in that region; later, the nails begin to show signs of atrophy and absorption—*sclerodactylia*—tactile sensation is markedly diminished and there is good deal of aching pain, especially at night. The digit is absorbed and telescoped into the next phalanx, so that in extreme cases, an entire finger may be lost owing to a process of rarefying osteitis. This pathological change, in some instances, commences at the base of the little toe and leads to spontaneous amputation of the entire member—*ainhum*—by formation of constricting band of fibrous tissue. The onset is insidious and the progress rather slow. The fourth toe may in some rare instances be affected but involvement of all the toes has not been recorded. *Ainhum* is less painful than *sclerodactylia*; a few of the patients do not complain of any subjective symptoms at all except in the last stage of the disease when the affected toe becomes gangrenous before dropping off.

Circumscribed patches of scleroderma with telangiectatic or purplish margin and atrophic centre are called *morphœa*. They begin as bluish red macules which soon change into depigmented, hard, dry, inelastic patches with smooth surfaces. The lesions may remain stationary or recover spontaneously. The small guttate variety of *morphœa* is sometimes called 'white spot disease'—which is a misnomer.

Treatment. The treatment of all types of scleroderma is very unsatisfactory. Every individual case should be carefully investigated both clinically and in the laboratory for any evidence of concurrent disease or active source of focal infection. Cases in which there is a good deal of hyperkeratosis respond to intensive thyroid treatment to a certain extent, but so far there is no drug which is known to check the over-productivity of the fibroblasts. Fibrolysin may be given a trial in 1 c.cm. doses intramuscularly every other day for 12 doses. Bi-weekly injections of muscle extract preparations such as 'sarcolan' or 'padutin' have been found very useful in many cases. Combined organotherapy with thyroid, suprarenal and gonad extracts produces considerable improvement in about 15 per cent. of cases. Syrup ferri iodide in 15 min. doses, iron and arsenic tonics and cod-liver oil are remedies of repute which sometimes cure by improving the general health of the patient.

WARTY GROWTHS (Verrucae). These are papillomatous, circumscribed hypertrophic lesions, gray or black in colour, in which the prickle cell layer grows to enormous thickness as also does the horny layer. Many of these have been proved to be infectious and auto-inoculable, especially the juvenile variety which is caused by a specific filtrable virus. Any place on the skin may be affected but on the scalp, face, lips and eyelids they are commonly associated with seborrhœic affection. Occurring on the soles of the feet, they render walking very painful and

simulate callosities, but unlike them, warts also grow in areas not subjected to pressure. They are roughly symmetrical and do not possess the soft core characteristic of corns. Several of these small outgrowths may fuse into one mass so that they appear as a single large hyperkeratotic surface. *Juvenile warts* usually remain as discrete, small, smooth, slightly raised papular lesions, the sites of predilection being the forehead, cheeks, nose, upper lip and backs of hands. They are of normal colour of the skin. *Seborrhæic or senile warts* are usually multiple slightly raised black keratoses and are found on seborrhæic types of skin showing senile trophy with age. These are usually covered with a greasy crust which on removal leaves a raw pulpy base. Some are extremely irritable and are sites of subsequent development of basal cell carcinoma. *Verruca acuminata* or venereal warts are associated with gonorrhœa and occur as multiple small pointed projections which multiply rapidly and form a large vegetating bunch on the penis, about the anus, on the mucous surface of the vulva and on the perineum. Rarely, they are seen in the axillæ, the groins, umbilicus or clefts of the fingers. They may grow to fairly large cauliflower-like masses and are sometimes very foetid owing to accumulation of the purulent discharge in the clefts between the filaments. The colour is usually pale yellow or pinkish.

Treatment. *Local.* Removal by curettage or excision is the simplest and best treatment for sparse discrete lesions, care being taken to thoroughly cauterise the base with pure carbolic, nitric or trichloroacetic acid or 20 per cent. silver nitrate to prevent recurrence. Hæmorrhage, secondary infection and scarring are the principal disadvantages. In extensive cases removal is not recommended. Refrigeration with carbon dioxide snow yields very satisfactory results provided each group is taken up separately under the applicator and frozen for about a minute or longer. The process is tedious and takes a very long time to establish a cure. Electrolysis and radiotherapy, separately or in combination, give most satisfactory results in extensive venereal warts, but a preliminary excision under anaesthesia may be necessary in some cases to expose the base to the effects of treatment and thereby prevent recurrence. Surgical diathermy is recommended especially for plantar warts but a single exposure to unfiltered X-rays brings about cure in most cases. All seborrhæic warts on senile atrophic skin should be examined histologically for signs of early malignancy and surgical treatment given accordingly.

Internal. Intensive thyroid treatment is of doubtful value and is not recommended except in combination with thorough local treatment. Proto-iodide of mercury in 1/6 to 1/4 gr. pills has been used but there appears to be no specific beneficial effect. Specific filtrable virus vaccines or autolysates have been tried at the Skin Clinic of the Calcutta School of Tropical Medicine with very encouraging results. To prepare the autolysate a freshly formed warty growth is removed entire under

strict aseptic precautions and emulsified in sterile normal saline, using finely ground sterilised pumice stone as the triturating agent. The emulsion is then filtered through an L3 Chamberland candle and the filter-passing virus is killed with 0.1 per cent. formalin. The filtrate is diluted and standardised so that 1 c. cm. contains 0.1 mgm. of the tissue material. Injections are given in gradually increasing doses every other day commencing from 0.1 c.cm., the maximum dose being about 0.5 c.cm. A course of six or eight injections controls the appearance of fresh crops and prevents relapses in young subjects. A few adults have responded very satisfactorily to this form of treatment. Bismuth salicylate has yielded very satisfactory results in rough types of warts; 2 c. cm. doses are given deep into the muscle twice weekly for eight doses and a second course is given after three months, if required.

MOLLUSCUM CONTAGIOSUM. As the name implies, this is a definitely infective hypertrophic lesion of the horny epithelium consisting of single or multiple, flat or rounded, greyish or flesh coloured papules, with a central depression containing a plug of caseous material—the molluscum body. In size they vary from a pin's head to a bean and the disease is most commonly found among school children who infect each other with the causative filtrable virus. The disease is sometimes met with in adults who pick it up from the Turkish baths, the barber's shop or beauty parlours. After an incubation period of 3 to 6 weeks, the initial lesions appear as very slightly raised papules about the size of a pin's head, with a depressed centre filled with curd-like mass composed of degenerated epithelial cells and keratin. Evolution is generally slow, the sites of predilection being the face, hands and genitals, although the entire body may be affected in very exceptional cases.

Treatment. It consists of manual expression of the individual molluscum bodies and touching up the cavities with pure carbolic acid by means of a fine camel-hair brush. They heal up in a week or so without formation of scars. The autolysate injections are useful and cure the patient in about 10 days.

Warty Growth of a Vegetative Nature but Soft to the Touch

ACANTHOSIS NIGRICANS. A rare disease characterised by hyperpigmentation and a warty condition of the skin of the neck, axillæ, genitals, groins, inner aspects of the thighs, flexures of the elbows and knees, umbilicus and anus. The face and the entire surface of the body are sometimes affected. The warty excrescences are very small and closely set and although the appearance gives an impression of a hard rough surface, the feel is quite soft and almost velvety to the touch. Similar lesions are occasionally seen on mucous membranes which become sodden and degenerated. Growth of hair and nails is markedly affected in extensive cases. Two clinical types have been described:—(1) The benign juvenile type which appears early in life and

occurs as isolated patches of vegetations, single or multiple but never with extensive or severe involvement of the skin. The general health continues good although the subject may feel very run down during periods of exacerbation. Complete involution may take place but the duration of the disease is of indefinite period. (2) The malignant type appears late in life and is commonly associated with the later stages of carcinomata of the internal organs. There is intensive involvement of widespread areas, the lesions being almost stationary without any periods of intermission. As a rule, they forebode a fatal termination within a short space of time. Involvement of the chromaffine cells is the principle ætiological factor in the malignant type which is brought about by pressure of intra-abdominal tumours on the suprarenals.

Treatment In the benign type of lesions, the best results are obtained by intensive local treatment with keratolytic ointments and plasters during the quiescent stage. Resorcin ointment 30 gr. to an ounce, salicylic acid ointment 1 dr. to 1 oz., or 10 per cent. salicylic acid plaster can be used with advantage. For small areas of limited involvement, carbon dioxide snow applied for 45 to 60 seconds can be used at 2 or 3 days, intervals. Periods of exacerbation call for general tonics, *e.g.*, iron, arsenic, quinine, calcium, etc. Any apparent focus of septic infection should be treated thoroughly at the same time. Residual hyperpigmentation requires local application of bismuth and perchloride lotion (mercuric perchloride. 1 gr., bismuth subnitrate 10 gr., pulv. tragacanth 4 gr., water 1 oz.) twice daily in combination with intravenous injections of pentavalent antimony compounds, *e.g.*, urea stibamine or neostibosan, the maximum single dose of these antimony compounds being 0.2 gm. Injection of bismuth salicylate or metallic bismuth in suspension is also worth trying.

PSOROSPERMOSIS OR DARIER'S DISEASE. It is characterised by symmetrical patches of papular dirty black warts affecting the neck, shoulders, face, the extremities, the front of the chest and the middle line of the back. It may sometimes spread over the entire surface of the trunk, buttocks, genitals, axillæ, gluteal crease, and behind the ears. Earlier lesions commence in the hair follicles as hypertrophic papules with greasy brownish-black crusts, and in course of time several of these coalesce to form large patches of malodorous, papillomatous growths which are intensely itchy and bleed readily. There is an offensive purulent discharge from the fissured and often ulcerated surface. The scalp is generally covered with greasy crusts. The lips are sometimes swollen fissured and ulcerated. Patches of keratosis and superficial ulceration of the tongue are not uncommonly met with. The nail beds show hyperkeratosis with malformation of the nails themselves. The palms and soles may also show patches of horny thickening.

Treatment. The treatment is very unsatisfactory and though the disease is a very rare one it runs a long protracted course, spontaneous

involution being unknown. Local sedatives and keratolytic ointments only afford temporary relief. Astringent dusting powders have been used empirically without much benefit. Best results have been reported by American authors from fractional doses of X-rays although intensive thyroid medication and non-specific protein therapy may be well worth a trial.

POROKERATOSIS. The disease is characterised by annular lesions with narrow elevated warty margins enclosing patches of slightly atrophied skin. They begin as small warty excrescences due to a chronic inflammation in the dermis and during evolution central atrophic skin becomes devoid of hair and sweating. Extension always takes place peripherally. The lesions are most pronounced on pressure and friction areas such as the hands and feet which are the sites of predilection of the disease. Any part of the body may be affected including the buccal mucous membrane where it appears as a white thick cord, the epithelium of the ridge becoming macerated by the saliva. The ætiology is not clearly understood although the disease is considered by some as being due to thyroid defect. There is a tendency towards familial incidence. The changes in the epidermis consist of hyperkeratosis and parakeratosis about the opening of the sweat ducts with infiltration of the corium about the sweat glands which undergo atrophy. Spontaneous involution may take place but, as a rule, the disease runs a chronic protracted course.

Treatment. Intensive thyroid treatment yields good results especially if combined with local application of 1 per cent. alcoholic solution of picric acid. Mild keratolytic ointment, *e.g.*, salicylic acid ointment 10-30 gr. to 1 oz., resorcin ointment 15 gr. to 1 oz., may have to be continued for a long time to prevent relapses.

Hypertrophic Lesions Involving the Connective Tissue of the Corium

PRIMARY. The lesions may be diffuse or circumscribed and are usually congenital in origin although in a few cases the first clinical sign is noticed in young adolescence.

DIFFUSE TYPE : DERMATOLYSIS. In this condition the skin and subcutaneous tissues are hypertrophic and loosely attached so that the skin hangs in folds. The neck, shoulders, face, thighs and scalp are usually involved. The skin is coarse, harsh and pigmented but the growth of hair and sweating are normal. The amount of hypertrophy and degree of looseness varies somewhat in individual cases and although the disease is of a slowly progressive nature, the growth is arrested after attaining a certain size. The ætiology is unknown. Except for the discomfort of the massive pendulous outgrowth the disease produces no symptoms.

Treatment. The treatment is surgical. Excision is not usually followed by recurrence.

CIRCUMSCRIBED TYPE. *Molluscum fibrosum*. The lesions consist of single or multiple flat, sessile or pedunculated tumour-like formations of varying sizes in the corium which may be present at birth or may be appreciable at about the age of puberty. A single growth may be very large and pendulous but multiple tumours vary a good deal in size. The majority of these tumours originate in the perineurium or the interstitial tissue of the peripheral nerves and those that are placed deep in the subcutaneous tissue are attached to the larger nerve trunks which are sometimes extremely painful owing to the pressure of these growths. The number of tumours may vary from half a dozen to several hundred and may present all the varied morphological appearances in the same individual. *Von Recklinghausen's disease* has been described as a separate clinical entity which is characterised by formation of numerous sessile and pedunculated tumours and massive areas of dermatolysis accompanied by patchy hyperpigmentation of the skin. The disease often runs in families and several members may be affected to varying degrees. There are no special symptoms.

Treatment is eminently unsatisfactory and surgical excision of individual pendulous growths is the only way of giving relief.

Acquired type. It is a very rare condition and has been found to occur during the later months of gestation. It consists of small tumour-like growths of soft consistency, mostly pedunculated, and affecting the front of the chest and mammary region. Spontaneous recovery takes place soon after child-birth.

SECONDARY. KELOID OR GROWING SCAR. Under ordinary conditions the fibrotic process leading to formation of scars is arrested by strangulation of the newly formed blood vessels in a healing wound and there is left pigmented or depigmented partly elastic scars which are stationary. If the formation of these new vascular twigs continues owing to abnormal response of the angioblasts, the growth of fibrous tissue also continues giving rise to hard depigmented overgrowths with claw-like processes extending well beyond the original site of injury. The epidermis over the keloid is thinned out from pressure and has a smooth glossy appearance with telangiectatic margins; the colour changes to brown in course of time and there may be a good deal of hyperæsthesia or actual neuritic pain owing to involvement of sensory nerves. The lesions vary a good deal in size and distribution, those occurring after burns or scalds being the most extensive and lead to contractures and disfigurement about the eyes or mouth. They rarely involute spontaneously although the growth may be arrested after some time.

Treatment. Best results are obtained in cases taken in hand early and treated by combined surgical and X-ray therapy. Old keloids are very resistant to X-rays or radium and plastic operation with skin grafting is the best remedy.

CORNS. These are circumscribed areas of horny thickening, conical in shape and produced by intermittent friction or pressure on the toes. The hard variety is formed on the external surfaces at the interdigital joints and has a shiny smooth surface, with the base of the cone upwards and the apex pressing on the subjacent soft tissues. Soft corns are formed between the toes and the hard surface is macerated owing to friction and sweating. They disappear spontaneously as soon as the cause is removed in the way of ill fitting or too tight footwear.

Treatment. Paring the corn down to the core and removing it with a sharp pointed bistoury affords instant relief. Painting the corns with salicylic acid $\frac{1}{2}$ dr., tincture cannabis indica $\frac{1}{2}$ dr., collodion 1 oz. for a week and then soaking in warm water brings out the entire corn with its core. Prophylaxis in the way of soft felt pads kept over the sites of pressure by adhesive ointment is of value. Sufferers must be warned that a too loose fit in shoes sometimes leaves the toes a good deal of freedom of movement in walking and thus induces growth of soft corns.

CALLOSITIES. These are hard circumscribed overgrowths of the horny epithelium over bony prominences subjected to intermittent pressure spread over a long time and differ from corns in that they do not possess a central core. They are very common on the palms of athletes and gymnasts or people handling implements of labour. Long hours of standing or walking on hard floors as in cases of shop walkers, is one of the important causative factors of callosities of the feet. Clinically, this condition is sometimes confused with plantar warts but the latter grow on areas not subjected to friction or pressure and possess multiple cores when the surface plaque of horny growth is shaved off. Callosities disappear spontaneously as soon as the cause of friction and intermittent pressure is removed; they rarely require any special treatment.

Atrophic Lesions of the Skin

PRIMARY. MACULAR ATROPHY. It is a rare disease of unknown ætiology of young adolescence, and usually commences as slightly reddish patches on the dorsum of the hands and the elbows. These patches are slightly oedematous and scaly but almost level with the surface of the unaffected surrounding areas and smooth to the touch, so much so that they may escape notice at this stage. The true skin is mainly involved, the epidermis remaining unaffected in the earlier stages. The distribution may be only local or symmetrical and regional; in very rare instances they are generalised. In course of time the atrophy is manifested by loss of elasticity and pliability of the skin; the normal lines of cleavage become exaggerated, and the surface epithelium becomes grayish, harsh and shiny. This pathological condition is due to replacement of the elastic fibres in the corium by growth of hard inelastic fibrous tissue which strangles the

sweat and sebaceous glands and hinders materially the nutritive lymphatic circulation in the epidermis and also the activity of the melanoblasts to a certain extent.

DIFFUSE TYPE. It is commonly associated with scleroderma but not with aetiological relationship with it. Lesions first appear on the dorsum of the hands and feet and slowly spread upwards to the arms, thighs, chest and back. The progressive involvement of the integument may be punctuated with periods of apparent improvement but complete involution never occurs. Affected subjects are extremely susceptible to changes in the atmospheric temperature and cannot undertake any physical exertion owing to atrophy of the sweat glands and consequent 'lack of cutaneous respiration.' Ulcerations and carcinomata often start from the atrophic patches.

LOCALISED HEMI-ATROPHY OF THE FACE. It is an extremely rare disease which occurs chiefly in childhood or soon after birth and trauma of insignificant intensity may be the exciting cause. There is shrinkage of all the structures on one side of the face, the affected side progressively become smaller and X-ray pictures reveal proportionate atrophy of the underlying bones as well. A few cases are associated with scleroderma. In exceptional cases the skin over the two malar bones only is affected leaving the other areas quite healthy.

Treatment. The treatment is very unsatisfactory in so far as there are no known remedies to check the progress of the disease. Administration of cod-liver oil combined with muscle extract injections are worth trying. Locally, inunction with olive oil or hydrous lanoline softens the epidermis and thereby improves the appearance of the skin to a certain extent. Patients should be warned against too frequent washing of the atrophic areas with soap and water and exposure to strong sunlight and harsh winds.

SECONDARY. This is seen after prolonged illness and is characterised by dry, smooth, shiny, grayish skin with atrophy of the hair and nails. The skin and its appendages generally become normal with the improvement of the general health but permanent alopecia and dystrophy of the nails is seen in a small percentage of cases. Linear atrophies with regional distribution result from various causes leading to rupture of the elastic fibres in the corium, e.g., pregnancy and lactation. The condition requires no special treatment.

Atrophy of the skin is sometimes noticed over the tender areas in neuritis and in paralysed limbs owing to involvement of the trophic nerves. Recovery follows improvement of the inflammatory or degenerative changes in the nerves supplying the affected area. *

Senile atrophy of the skin is seen in the aged people. The elasticity is lost, the skin becomes wrinkled, thin, glossy and telangiectatic. Sometimes a diffuse brownish discoloration and leathery thickening is met with. The appendages also undergo atrophy; warty growths begin to

appear on the face, back of the hands, chest and back and carcinomatous changes supervene on these warts later.

Atrophy following other skin affections, *e.g.*, lupus erythematosus syphilis, tuberculosis, leprosy, etc., hardly calls for special mention.

Abnormalities in the Colour of the Skin

LEUCODERMA OR WHITE SKIN. *Congenital.* Complete failure of the basal cells in oxidising and storing melanin results in albinism which, as a congenital condition, is associated with white hair and pink eyes. The skin may show a few dark freckles and *tache de Morgan* or discrete small blood-moles, which are often the seats of epitheliomata later in life. The subjects are extremely susceptible to sunlight and suffer from chronic solar dermatitis on the exposed parts, namely, the face, hands and feet. They should be kept away from strong sunlight as much as possible as there is no cure for congenital albinism. A milder degree of this condition is sometimes seen as congenital error in pigment drift resulting in a 'spotted skin' or actual *piebaldism*. The colour of the hair and iris usually remains true to the racial character of the patient. Slight errors sometimes correct themselves with the attainment of maturity especially in women after child birth. Both white and dark races are affected but it is more noticeable in the latter.

Treatment is of very little efficacy. Addition of larger quantities of peas, beans, pulses, soaked gram, etc., have yielded some good results after prolonged use but probably the improvement is spontaneous in such cases.

ACQUIRED PRIMARY. The age of incidence is during young adolescence, the disease rarely commencing under 2 years or above 60. Any part of the body may be affected, including the muco-cutaneous areas. It usually begins insidiously as a small depigmented herald spot which may be diffuse or sharply circumscribed. Several spots may appear on different parts of the body at the same time and the progress is so rapid in some cases, that the major portion of a limb, trunk or face may become dead white in the course of a few months. Usually the spread is rather slow and spontaneous involution and complete recovery is not very uncommon. Four clinical types are met with namely, (1) *melung type* affecting the palms and soles only; (2) *muco-cutaneous type* affecting the lips and angles of the mouth, the eyelids, the anus, the prepuce and the vulva; (3) *'dholi'* and *'sari'* type affecting the pressure area about the waist where cloth is worn by Indians; (4) *generalised type*. Any particular case may show two or more of the clinical types of lesion. About 20 per cent. of patients give a history of dysentery; a few start after protracted illnesses like typhoid, pneumonia or chronic dyspepsia which is probably of bacillary dysenteric origin. Leucoderma is hardly ever seen in kala-azar patients.

Treatment. Medicinal. In view of the fact that the digestive tract is the most important manufacturing centre of the vegetable amine substances from which melanin is produced and stored in the skin, it is advisable to give the patients 'intestinal antiseptics' for prolonged periods and correct all errors of digestion. The following have been used at the skin clinic of the Calcutta School of Tropical Medicine with success.

(i) Mist. hydrarg. perchlor. in 1 oz. doses twice daily after food, (ii) salicin 10 gr. twice daily after food, (iii) hydrarg. cum creta 1 gr., pulv. ipecac 1 gr. twice daily after food, (iv) zinc sulphocarbolat 4 gr. has been tried in a few cases but the drug causes gastro-intestinal irritation after prolonged use, (v) emetine hydrochloride 1 gr. intramuscularly, one dose is given every day for six consecutive days with a view to partially depressing the function of the suprarenals. The patient should not be allowed to take any physical exertion during the course of emetine treatment on account of the depressing effect of the drug on the heart. The importance of latent foci of infection in the bowels should not be lost sight of and wherever possible every patient should have his stools examined for protozoal, helminthic and bacterial infection, and specific treatment given according to the findings.

Local. Of all the drugs that have been used, oil 'Bouchi' (*Psoralea corylifolia*) has yielded the best results. The oil should be applied on leucodermic spots with gentle friction, preferably at night, as the irritating action may be intensified by solar rays. The application can be repeated during the day according to tolerance. Some people are extremely sensitive to oil of 'bouchi' and sparse application results in intense inflammatory reaction and blistering of the skin. The oil should be used suitably diluted with olive oil in such cases and can be combined with 10 gr. of ichthyol to an ounce of the dilute oil.

Diet. High protein diet is recommended for cases of leucoderma. Peas, beans, pulses and dal should be given in increased quantity. Gram seeds soaked in water over-night may be given raw the next morning. Carrots are also beneficial on account of its rich pigment content.

Prognosis is unfavourable in the melanic and muco-cutaneous types. Cases of over five years standing do not respond to treatment owing to almost permanent loss of function of the melanoblasts.

ACQUIRED SECONDARY. Any ulcerative lesion of the skin leaves depigmented scars if the loss of substance involves the corium and consequently damages the melanoblasts. Burns of the second degree, lupus erythematosus, lupus vulgaris and tuberculides, ulcerative syphilides and yaws and granuloma inguinale, all leave permanent white scars which can be masked to a certain extent by carefully handled tattooing. The important non-ulcerative lesions are the first stage of dermal leishmaniasis, the third stage of leprosy, advanced stage of leukaemia, and syphilis in the late secondary and tertiary stages.

Treatment should be directed towards the underlying cause as leucoderma is only a symptom in these affections.

CHLOASMA OR DARK SKIN. *Congenital:* Generalised dark colour of the skin can hardly be considered as a malady but single or multiple patches, occurring in different parts of the body cause very bad disfigurement especially on the face and neck. Localised chloasma of this type occurs commonly in the sacral region of new-born babes and is known as a *mongolian spot*; the colour is bluish on comparatively darker skin, almost purple in fair children, and black in extreme cases. The centre of the patch is the darkest and the edges fade into the general colouration of the skin. After persisting till the 5th or 7th year of life mongolian spots disappear spontaneously. Congenital flat moles, when diffusely extensive, may resemble chloasma but careful observation shows that they grow slowly with age and are more sharply circumscribed without fading margins.

ACQUIRED PRIMARY. Generalised darkening of the skin is seen in a very small percentage of cases after puberty owing to the recessive individual character becoming dominant. Bronzing of the skin is sometimes noticed during gestation and in old age due to disturbance of the suprarenal function. The normally hyperpigmented areas become more accentuated and the muco-cutaneous surfaces also become pigmented. There is no special treatment for the chloasma of pregnancy as the pigmentation disappears soon after child-birth. Senile bronzing is usually slowly progressive in character, and is sometimes associated with a low blood pressure.

LOCALISED. *Chloasma vulgaris* or the common type is seen on the malar prominences, the bridge of the nose and the forehead. The spots are usually oval or rounded in outline and the margins fade into the colour of the normal skin. The colour varies from light yellow to almost black, several small patches often coalescing to form a fairly large one on the face. There are no subjective symptoms. Any part of the body may be affected including the mucous membranes in extensive cases. The disease is more common in women in the early forties and is correlated with the retrograde changes of the climacteric suggesting abnormal physiological functions of the ovary and suprarenals.

TREATMENT consists of using bleaching lotions and creams which induce slow desquamation of the horny layer and shedding of the pigment particles along with it. The general health should also be well looked after and fatigue and overstrain are better avoided. Best results are obtained by combining local treatment with organotherapy, extracts of thyroid, suprarenal and gonads offering the most suitable combination. The following line of treatment have been found most efficacious for common chloasma:—Lotion containing mercuric chloride 1 to 2 gr., bismuth subnitrate 10 gr., tragacanth powder 5 gr., water

1 oz., to be painted on dark patches. Salicylic acid 15 gr. can be combined with an ounce of this lotion. Internally, ext. thyroid sicc. $\frac{1}{6}$ gr., ext. suprarenal sicc. $\frac{1}{2}$ gr., ext. orchic subst. sicc. $\frac{1}{2}$ gr., ext. ovarii sicc. 2 gr. is given for female patients. For male patients ext. orchic subst. sicc. is given in 2 gr. doses and the ext. ovarii sicc. is reduced to $\frac{1}{2}$ gr. The powder should be taken twice daily on an empty stomach.

ACQUIRED SECONDARY. Localised patchy and diffuse hyper-pigmentation of a secondary nature appears at sites of friction and irritation from diverse sources. The most important physical agents are heat and sunlight, the hyperpigmentation in such cases being preceded by erythema. Mechanical pressure and friction of clothes, *e.g.*, wearing the 'dhoti' and 'saree' round the waist, pressure of truss pads, garters, braces, the back and front collar studs, etc., produce dark patches at the sites of contact with the skin; cure is spontaneous, though somewhat slow, as soon as the cause of irritation is removed. Trauma either mechanical or resulting from violent irritative lesions like scabies and prurigo, leave the skin somewhat hyperpigmented especially in subjects who are hypoadrenic in their endocrine balance. Seborrhæic dermatitis also induces patches of chloasma on the forehead, cheeks, nose and face generally, and in some cases all over the body in hypoadrenic subjects. Treatment of the primary cause brings the colour of the skin back to normal. Intra-abdominal tumours of a malignant nature, Addison's disease and Grave's diseases cause generalised or diffuse chloasma, the mucous membrane of the mouth and tongue also show black patches fairly early in the course of these disease. Rheumatoid arthritis, and tertiary lesions of syphilis also cause hyperpigmentation of the skin.

XERODERMA PIGMENTOSUM. It is a very rare and invariably fatal disease characterised by parchment-like atrophy of the skin with occurrence of numerous hyperpigmented patches on the face, scalp, neck, forearms, backs of hands and other exposed parts of the body. Three distinct stages of this affection have been described and in the vast majority of instances the disorder is apparent before the end of the first year of life. In the first stage, persistent erythrodermia of the exposed parts even after short exposures to sunlight followed by slight puffiness and roughness of the skin are the most prominent symptoms. The skin develops a mottled appearance owing to a diffuse angiomatous condition of the capillaries. The second stage commences about the third year of life with abatement of the erythrodermia and appearance of large number of freckle-like spots and scaling of the skin of the affected areas. A few flat warts also make their appearance. The conjunctivæ become markedly hyperæmic and there is photophobia. During the third stage white depigmented spots with telangiectatic borders appear between the pigmented areas, the warty growths become very numerous and in the course of another year or so many of the

warts undergo malignant changes. Several of the pigmented spots may coalesce to form fairly large patches and the affected areas assume a peculiar sepia colour. The sweat glands undergo partial atrophy but the sebaceous glands are not affected. Owing to the atrophy of the corium and excessive formation of horny epithelium, contractures of the nose and mouth, ectropion with ensuing corneal ulcers are frequently met with. The disease is essentially a familial one, two or more children being affected in the same family. The causative factor is probably a congenital or inherited susceptibility or predisposition which results in abnormal response of the skin to stimulation with certain of the rays in the solar spectrum.

Treatment. Best results are obtained from prophylactic measures in the first stage of the disease. The exposed parts should be covered with an ointment containing 5 per cent. of di-sodium-naphthol sulphonate which absorbs the ultra-violet rays. X-ray and radium therapy has been recommended for the second and third stages.

Prognosis is very unfavourable; the progress of the disease is usually rapid and the patient dies of generalised carcinomatosis before he reaches the second decade of life.

Diseases Affecting the Vascularity of the Skin

ERYTHEMATA. Simple transient erythema is produced by external agents like heat, sunlight, chemical and mechanical irritants, and they act by producing dilatation of the capillaries. Spontaneous recovery is the rule as soon as the cause is removed. The most important internal cause is psychic or emotional as is seen in blushing. Permanent dilatation of the capillaries may follow the action of the external agents over a long period in a subject whose capillary tone is poor. Hypotonic condition of the capillaries may be due either to toxic absorption from focal sepsis or to inherent hypo-pituitary and hypo-adrenic conditions. Defective calcium metabolism is also an important aetiological factor. The important clinical varieties are:—

(1) *Erythema rubra nasi* or *facial erythrodermia*. The nose, cheeks, forehead and the neck assume an unusually flushed appearance without any apparent cause. There are usually no subjective symptoms. Patients may show marked erythrodermia of the hypothenar eminences of one or both hands. In a certain percentage of cases a very fine telangiectatic condition of the alae nasi and the cheeks is noticed.

(2) *Erythema ab igne*. This is caused by a permanent dilatation of the capillaries and arterioles induced by prolonged exposure to excessive heat. It is almost exclusively seen in cold countries, more often in women than in men, and affects the anterior tibial region of both legs which are exposed to the radiant heat of stoves or ovens. In the early stages the skin has a pink mottled appearance, but with the onset of reticulated erythema of the later stages, a certain amount of pigmentation

supervenes, so that a patch may shew simultaneous variation from pale pink to purplish dark brown. Too frequent use of the hot water bag may produce these vascular changes at the site of application.

TREATMENT. The first essential is to remove the cause. Locally, cooling soothing lotions, *e.g.*, calamine lotion should be used as a continuous application. For facial erythrodermia a 5 per cent. ointment of disodium naphthol sulphonate should be used when going out in the sun. Internally, calcium lactate 10 gr. with parathyroid 1/10 gr should be given twice daily on an empty stomach.

(3) *Erythema pernio or chilblains.* The papillary capillaries undergo marked dilatation with cold, and the permeability of the endothelium is increased allowing exudation of serum in the papillary layer. The exposed parts like the fingers, toes, ear and nose are usually affected, some people being more susceptible than others. Cold feet during winter months is the most important predisposing cause but under-nourishment and defective calcium metabolism are no less important factors in producing the disease after exposure to moderate cold. The affected areas are red, sometimes bluish owing to venous engorgement, swollen and extremely irritable but quite cool to the touch, and often covered with sweat. There is good deal of pain and burning owing to the papillary oedema, which in extreme cases interferes with rest at night

TREATMENT. Local. The affected parts should be bathed in warm water 4 or 5 times a day and massaged gently with plain lanolin or simple ointments. The feet should be kept dry and warm and exercised to improve the circulation. Warm Goulard's lotion is useful in relieving the pain and burning. The inner side of the socks should be well powdered with camphor and French chalk (camphor gr. 30 to 1 oz of French chalk) before putting them on.

Internal. Calcium lactate 10 gr. with parathyroid 1/10 gr. should be given twice daily on an empty stomach. Other calcium salts, *e.g.*, calcium gluconate, colloidal calcium, etc., are of proved efficacy. In severe recurrent types of cases intramuscular injection of colloidal calcium, or intravenous injection of calcium chloride in 5 or 10 per cent solution may be required. A diet of high vitamin contents and general tonics are recommended. Local or general ultra violet radiation, when available, brings about quick amelioration of symptoms.

TOXIC ERYTHEMAS. Generalised. Certain toxic substances having their origin in bacterial activity in a focus of sepsis or derived from the end products of protein digestion in the intestines, are absorbed into the circulation and produce dilatation of the different vascular plexuses at the different levels in the skin. Depending on the level of activity and "iso-electric points" of these substances, there may be produced simple erythema, erythema with oedema of the skin and epidermis; or erythema with bullous formation. Inflammatory changes may

also occur in the corium. The distribution of the lesions may be local, general or universal, in which last case the mucous membranes are also affected. The extent and distribution varies a good deal, the eruption itself being made up of pin-head sized red macules which are generally so closely set as to form fairly large irregular patches all over the body. The trunk, upper arms, thighs and face are the sites of predilection with a tendency to involve the hair follicles. Clinically, some toxic erythematous rashes often bear a close resemblance to scarlet fever (*E. scarlatinae*) or measles (*E. morbilliforme*) but are not associated with fever or other general toxic symptoms. Localised macular rashes may, in rare instances, be ushered in with rigor, joint pains and fever of short duration and have to be differentiated from 'filarial fever' by the absence of lymphangitis, local pain and tenderness. Recurrences are not very uncommon, a few cases showing definite periodicity in these attacks. There is a feeling of heat and tension of the affected skin and desquamation of the surface epithelium sets in as soon as the erythema has subsided.

Treatment. During the attack, the patient should be kept in bed and elimination aided by suitable aperients and diuretic mixtures. A complete change of the diet is very helpful. Locally, frequentunction with 0.5 per cent. carbolic olive oil or calamine lotion with 10 per cent. glycerine relieves the burning and tense feeling of the skin. Internally, calcium salts either singly or in combination with parathyroid can be used to tone up the fine arterioles and capillaries of the upper layers of the dermis.

Recurrent cases require thorough investigation regarding the presence of latent focal sepsis in the tonsils, teeth or bowels. The urogenital tract may also harbour such foci, especially in women. The curative treatment has to be carried out according to the nature and site of the infection; surgical interference may be necessary for apical abscesses, septic tonsils or cervical erosions. General tonics and change of climate are recommended when repeated attacks seriously undermine the health.

Erythematous Lesions accompanied with Inflammatory changes in the Skin

ERYTHEMA MULTIFORME. Acute. As the name implies, this disease is characterised by protean local lesions consisting of red macules, papules, plaques and vesicles, generally of symmetrical distribution. They usually start as small erythematous herald spots slightly raised above the skin surface which, in the course of 24 hours, enlarge into large papules, or plaques; the inflammatory process is often of great intensity so that large blebs, filled with serous, pustular or even hæmorrhagic exudate, form within a few hours. The papillary and sub-papillary plexuses show a good deal of dilatation with exudation of

serum and perivascular inflammatory infiltration. There is oedema of the cutis with accumulation of serum underneath the epidermis, the entire thickness of which may be lifted up to form the bleb; leucorrhæxis or erythorrhæxis is seen in very acute cases. The sites of predilection are sides of the neck and face, the dorsal surfaces of the hands, forearms, feet and legs and in very exceptional cases the mucous membrane of the mouth is also affected. The lesions are bright red in colour fading on pressure, and gradually changing into a purplish tinge at the periphery. The disease may be self-limited lasting for a short time or it may be prolonged for months or even years. Constitutional symptoms are generally absent, except in cases with acute onset, but pain and irritation are generally present at the site of the lesions. The general health may remain good, but in chronic cases it is much impaired. There is a certain amount of diversity of opinion regarding the ætiology—the generally accepted view is that it is an allergic condition due to toxic absorption from the gastro-intestinal tract which may be derived either from bacterial infection of the intestinal mucosa or from the end products of digestion of animal food. The important clinical types are *erythema papulatum*, *erythema tuberosum*, *erythema bullosum*, *erythema iris*, *erythema marginatum*.

Treatment. During the attack, the treatment is mainly symptomatic. Patients should be kept in bed and have all physical exertions curtailed. The diet should be light and plainly cooked and the animal foods reduced to a minimum. The kidneys should be well flushed with large drinks of water and the bowels stimulated with mild aperients. Locally, calamine lotion or liniment is the best application in all stages of the disease. Fully-formed blisters should be punctured aseptically and dressed with a dusting powder consisting of equal parts of zinc oxide and starch with 1 per cent. of aristol by volume. Internally, salts of calcium are given either singly or in combination with parathyroid, iron, arsenic and strychnine tonics are indicated where the general health is poor. All stimulating drinks and beverages are to be withheld. The following are the important investigations which help a radical cure :—

- (i) The peripheral blood is to be examined to determine a true rise in the eosinophile population which is always indicative of 'animal protein leak' into the circulation.
- (ii) Dermal sensitiveness test with food extracts to eliminate those articles from the dietary which are inducing the 'allergic state.'
- (iii) Serial examination of the stools for evidence of protozoal, helminthic or bacterial infection so that specific treatment may be given according to the nature of positive findings.
- (iv) Examination for other foci of sepsis, namely, in the teeth and the maxillary and nasal sinuses, the throat and tonsils, and the cervix uteri in female patients.

URTICARIA. This disease is characterised by development of white, pink or red wheals of short duration, accompanied by itching and feeling of burning in the skin. The individual lesions vary a good deal in size, are rarely defined and contiguous lesions very often coalesce to form large plaques with an erythematous halo around them. After persisting for a few hours the wheals disappear spontaneously to reappear almost with clock-like regularity the next day. The total duration of the disease generally does not exceed ten days to a fortnight but in some cases it may persist for months or even years. The onset is sudden and in the majority of cases unaccompanied with prodromal symptoms. Any part of the body is liable to be affected including the mucous membrane of the larynx, and this in intensely acute cases, constitutes a source of danger to the life of the patient. In cases of moderate severity the skin resumes a normal appearance after the wheals have subsided but the blood vessels may remain in a state of imbalance so that stroking or pressure may produce a large welt. These cases show 'dermographism' which can be provoked by any blunt-pointed article, the tip of a penholder, for example. Areas of pressure from garters or waist bands may stand out as thick welts as soon as these are removed. Sometimes the attack is so sharply intense that bullae form on the wheals. Clinically, this condition is known as *urticaria bullosa* and the contents of these blisters are, in rare instances, filled with purulent fluid—*urticaria pustulosa* or with blood—*urticaria hemorrhagica*. Localised papular type of urticaria, *urticaria papulosa*, is seen on normal pressure areas, namely, the buttocks and back in badly nourished children. A chronic variety, *urticaria perstans*, has also been described.

The ætiology is essentially an allergic phenomenon produced by the end products of digestion of some animal protein food which the patient is not accustomed to take, or the end products of the average daily protein food against which the system develops a sensitiveness. Shell fish and tinned or canned foods are by far the commonest causes of acute urticaria. Lesions of the bowels due to chronic amoebic or bacillary type of infection play a very important part in allowing the 'amines,' derived from the digestion of animal food, to leak into the circulation and produce their toxic actions on the capillaries and arterioles in the papillary and sub-papillary plexuses. Injection of animal sera and ingestion of some drugs are sometimes followed by acute urticarial eruption. In a few rare instances physical agents like heat and light and diverse psychic and emotional conditions have been known to bring on an attack.

• The wheals are produced as the result of acute dilatation of the papillary and sub-papillary plexuses with a good deal of exudation of serum in the pars papillaris. There is inflammatory perivascular exudation, which latter is most intense in the region of the sweat glands. This dilatation is due to (1) failure of the constriction effect of the

sympathetic fibres in which case there are other evidences of hypo-adrenic condition and eosinophilia; (ii) sustained parasympathetic effect of almost persistent dilatation without any evidence of hypo-adrenia or rise in the eosinophile population.

Treatment. Locally, during the attack, cooling soothing lotions, *e.g.*, calamine lotion, equal parts of rectified spirit and water, 0.5 per cent. carbolic lotion, are useful in relieving the irritation. Iced fomentations are required when the plaques are intensely acute in onset the bullous formations may be aborted by this measure.

The general management of a case calls for an immediate examination of the blood film of the patient for evidence of eosinophilia in which case adrenalin 0.2 c.cm. combined with pituitrin 0.3 c.cm. should be given intramuscularly at once and repeated for the next three consecutive days. Ephedrine in $\frac{1}{2}$ to $\frac{1}{4}$ gr. doses can also be given by the mouth twice daily for 3 to 5 days.

A careful survey of the dietary is required to eliminate any unusual animal food like shell fish or oysters (which are hardly ever eaten in India) or tinned meats. In the absence of a definite history, sensitiveness of the skin should be tested against extracts of protein foods which constitute the patient's average daily diet, and those items which produce a 'nettle rash' lesion on scarified skin are completely omitted for three weeks. This test sometimes shows a positive reaction to all the extracts used (generalised sensitiveness) and too much importance cannot be given to dietetic restrictions in these cases. A small dose of calomel (2 gr.) followed by a saline cathartic the next morning is very useful as a routine measure in robust subjects. Cases which show very high eosinophile count in the blood are best treated with soamin injections, twice weekly. About eight injections are required, the total quantity of soamin used being about 16 gr. Other arsenical preparations can be given by the mouth but the response is usually slow. Cases which do not show any rise in the eosinophile population should be treated with drugs which act as depressants to the sympathetic nerves, *e.g.*, emetine hydrochloride 1 gr. intramuscularly on 6 consecutive days. Aspirin, belladonna and derivatives of barbituric acid are also of use in this type of case. Every case should have a thorough investigation into the condition of the bowels and latent amœbic or bacillary infections detected by repeated examination of the stools in the laboratory, so that specific treatment can be given at an early date. Internally, calcium lactate 10 gr. with parathyroid 1/10 gr. is given twice daily for toning up the capillaries. The adrenalin and pituitrin injections can be followed up with a course of 'mixed gland products' (thyroid 1/4 gr., suprarenal 1/2 gr., gonad substance 2 gr., given twice daily on empty stomach) for three weeks. A small percentage of persistent refractory cases sometimes respond well to injections of peptone, auto-hæmo or auto-sero-therapy.

GIANT URTICARIA OR ANGIO-NEUROTIC OEDEMA. It consists of localised deep oedema of acute and sudden onset and generally affects one limb or a part of the face. There are hardly any prodromal symptoms, the patient wakes up in the morning with a hand or foot or one side of the face enormously swollen accompanied with a feeling of toughness and sometimes pain. After persisting for two to five days the swelling subsides but may recur in the same or some other part of the body. The affected part looks red and inflamed but is cool to the feel. A few cases persist for days together and in rare instances different parts of the body may be affected one after the other without any abatement of the first lesion. The ætiological factor is the same as that of ordinary urticaria, the only difference is that the deeper plexuses are involved in giant urticaria and the exudation takes place in the deep fascia.

Treatment. The same line of investigation and treatment is adopted in both urticaria and giant urticaria.

URTICARIA PIGMENTOSA. It is a chronic inflammatory disease of the skin in which the lesions commence as acute urticaria but instead of subsiding within a few hours, persist indefinitely and undergo pigmentary changes. The individual lesions are firm, well defined wheals with an erythematous halo. They are pale in colour in the beginning and after a week or so become chamois coloured, brownish and then almost black. Contiguous lesions may coalesce to form a fairly large plaque type of lesions. There is good deal of itching as a rule, but a few cases do not complain of any irritation at all. It usually begins in early infancy or within the first decade of life and persists for some time. Spontaneous recovery takes place in a fairly large number of cases. Any part of the body may be affected but the trunk hardly ever escapes. Cases with intensely acute onset may show bullous formation. Crops of new lesions develop from time to time while the older ones gradually subside leaving atrophic spots or scars. Very little is known about the ætiology. Histologically *urticaria pigmentosa* shows perivascular infiltration with mast cells instead of leucocytes as in the case of ordinary acute urticaria. As a rule the disease disappears spontaneously with the onset of puberty. It has been suggested that adults with a persistent thymus sometimes develop *urticaria pigmentosa*. The general health remains good. Treatment is very unsatisfactory. Of the various remedies that have been tried, pilocarpine and atropine give best results. The itching has to be treated with antipruritic lotions and creams. Deep X-ray therapy of the thymus region has been tried with a certain amount of benefit but it is doubtful whether the results of such treatment are permanent.

PITYRIASIS RUBRA OR EXFOLIATIVE DERMATITIS. This is an acute or sub-acute inflammatory disease generally affecting the

entire surface of the skin which becomes red, and is accompanied with good deal of desquamation of the surface epithelium. An attack may be ushered in with slight rise of temperature, malaise or gastro-intestinal disturbances, but in majority of cases it begins suddenly as symmetrical localised patches which are pinkish or red at first and slightly rough to the feel. In the course of a few days the colour changes to dark red, the individual lesions tend to spread and become covered with thin, loosely adherent, flaky, grayish scales which are usually small on the exposed parts like the face and hands, but are of fairly large size on the covered areas of the body. These localised patches may heal spontaneously after 3 to 5 weeks but recurrence is almost the rule, and greater areas are involved with each recurrence till the entire surface of the body is affected. There is very little œdema or thickening of the skin in the early stages of the disease, but these changes become more and more marked with each relapse. Excepting for a few cases of intensely acute onset, there is no oozing of serum and bullous formations are never seen at any stage of the disease. During exfoliation, the thick horny layer of the palms and soles may come off as glove-like casts. The hair and nails are markedly affected and both may be shed in the latter part of the ailment. There is little or no itching in the early stage but the skin is extremely tender and sensitive to changes in the atmospheric temperature and solar radiation. A feeling of toughness and tension is always complained of by the patients. The skin may remain pigmented for a long time after recovery. Long-standing cases may develop permanent alopecia, onychia and dysidrosis owing to fibrosis of the corium and atrophy of the sweat glands.

The ætiology has been the subject of a good deal of controversy, but in the experience of the Skin Clinic of the Calcutta School of Tropical Medicine the disease has been classified as allergic in origin. A very large percentage of cases show focal infection in the bowels with imbalance of the endocrine functions owing to the chronic toxic absorption. Almost all cases shew hypo-function of the suprarenals. The histological changes are confined only to the subpapillary layer, the papillæ themselves are enlarged and somewhat elongated with moderate infiltration. The inflammatory exudate is most marked in the region of the sweat glands in chronic cases, which explains the permanent anidrosis after recovery.

A few cases have been known to terminate fatally with symptoms of general toxæmia after repeated attacks involving the whole body.

Treatment. The treatment is mainly symptomatic during the first onset. The skin should be kept moist and pliable with continuous application of plain olive oil or liquid paraffin. For the excessive redness of the skin calamine lotion is the best local application which can be combined with liq. plumbi subacetatis fortis, 5 min. to every ounce, provided there is not much oozing. The weeping is best controlled by bland dusting powders like kaolin or a mixture of equal parts of starch

and zinc oxide. The patient should take a warm bath, preferably in the morning, without using any soap, and be at rest as much as possible during the day. Exposure to sunlight is to be avoided. A thorough investigation into the presence of latent foci of infection, especially in the bowels, is to be undertaken as early as possible so that specific treatment can be given according to the nature of the infection. A total and differential count of the leucocytes in the peripheral blood is helpful and cases with a marked rise in the eosinophile population respond well to arsenical preparations which can be given either as Fowler's solution or Donovan's solution in 2 to 5 min. doses twice daily after food. Stovarsol or carbarsone may also be given for a short period not exceeding 7 to 10 days. The dilatation of the blood vessels is due to lack of sympathetic tone and hypoadrenia. This condition is best treated with pentavalent antimony compounds of which neostibosan (von Heyden 693) gives the best results. The dosage is 0.1 gm. gradually increasing to 0.5 gm., intravenously; one injection is given every day for 10 consecutive days. As a rule the drug is tolerated well but it is advisable to take the usual precautions against the untoward effects of intravenous therapy of heavy metallic salts by examination of the urine for albumin and casts. The dose is of course regulated according to the patient's body weight and general build. The bowels and kidneys should be kept functioning, the diet should consist of plainly cooked and easily assimilable foods. Alcohol and other stimulating drinks are contraindicated. The patient may require general tonics for the run-down condition of his health, for which quinine, iron, arsenic and cod-liver oil have been used. In long standing cases secondary thickening of the skin is treated with keratolytic ointments and paints containing resorcin, salicylic acid, acetic acid in a suitable proportion which is not too strong and irritating to the skin of the patient.

ECZEMA. It is a symptom complex of any chronic dermatitis and not a disease *sul generis*, as the symptoms and pathological changes are found in most of the chronic inflammatory diseases of the skin. It is characterised by four cardinal symptoms, namely, pain and irritation, redness, heat and swelling of the part affected. Clinically, two types are met with, the dry and weeping eczemas. The principal underlying cause of this syndrome is the response of the superficial cutaneous plexuses to external and internal stimuli which may be latent or apparent. The lesions begin as localised papular or vesicopustular eruption with a good deal of inflammation and infiltration of the true skin. These vesicles often burst and keep oozing serum—hence the name 'weeping eczema'. After persisting for some time, which may be prolonged to several months, there is a certain amount of abatement of symptoms, but the affected area remains thickened and harsh. Recurrence is very common and secondary changes in the skin begin to appear with each fresh attack. These changes may

involve the texture of the epidermis and the dermis as well as the pigmentation of the skin. Complications arising from secondary infection of the vesicles with pyogenic cocci are very common and completely alter the clinical picture in majority of cases. The aetiology is obscure in most cases. The lesions are caused by dilatation of the papillary and interpapillary capillary twigs with oedema of the papillae and the rete accompanied by perivascular inflammatory exudate.

It has been observed that the two main factors concerned in the production of a protean lesion like eczema are (i) external parasitic infection, and (ii) the susceptibility of the skin affected. In this country ringworm and seborrhoea are the two commonest primary infections of the glabrous skin and also scabies, especially in children. Secondary infection with streptococci and staphylococci are concerned in the production of induration of the skin, oozing of serum and formation of pustules. The vulnerability and susceptibility of the skin depends on the fineness of texture of the epidermis and is controlled by the activity of the endocrine glands which, incidentally, is a racial or familial trait. It is for this reason that some eczemas tend to run in families. On the other hand, this susceptibility may be due to acquired allergic conditions following focal infection, especially in the bowels, or sensitiveness towards some particular kind of animal food. Chemical and other irritants acting on one particular area of the skin for a long time produce local kataphylaxia and thus enhance the acquired susceptibility.

Treatment. The treatment has to be undertaken in three stages. First of all the secondary infection is to be treated with local applications according to the nature of the infecting organism. Staphylococcal infection requires antiseptic baths and compresses with 5 per cent. boric lotion, lysol lotion 1 in 20 or chinisol solution 1 in 100, after which 5 per cent. gentian violet solution in 20 per cent. alcohol should be applied night and morning. Autovaccine therapy may also be tried, although it is not of any great curative value. Streptococcal infections should be treated with continuous applications of cooling evaporating lotions of which calamine lotion is the best. Cold compresses with 1 in 3000 acriflavin lotion is also of benefit. Autovaccines are very useful in reducing the induration and deep inflammation of the cutis. When the secondary infection is cured the primary infection can be treated with Whitefield's ointment, ringworm paint or sulphur lotion according to whether it is ringworm or seborrhoea. The peripheral blood should be examined for evidence of eosinophilia and the stools examined serially to detect chronic amoebic or bacillary type of dysenteric infections so that specific curative treatment may be given to control the susceptibility of the skin. The diet should be regulated especially in cases of extensive streptococcal infection; sensitiveness towards any particular kind or group of food materials should be carefully investigated and the offending items eliminated. Internally, general tonics with quinine,

iron and arsenic may be helpful; endocrine therapy is indicated in cases showing signs of hypo-function of the thyroid, pituitary, suprarenals or gonads.

DERMATITIS REPENS OR ACRODERMATITIS PERSTANS.

This is a subacute or chronic inflammatory disease of the skin and is characterised by patches of raw glazed-looking denuded rete surrounded by a slightly elevated, ragged or irregular undermined edges formed by the broken horny epithelium. A fair amount of serum or pus can be squeezed from the undermined edges. The disease usually begins at the site of some minor trivial injuries as a red erythematous patch with formation of vesicles, within a day or two after the initial abrasion. These vesicles soon rupture and give rise to the characteristic lesions which tend to spread peripherally. The disease is more commonly seen on the fingers but occasionally on the toes and soles of the feet. A few cases occur without any primary injury. It is slowly progressive in character but healing generally takes place at the centre of the lesion more rapidly than the spread at the margins. Constitutional symptoms are absent and local pain and itching is almost negligible. The aetiology is rather obscure but in majority of cases it is due to a condition of kataphylaxia or loss of the defensive power of the tissues against pyogenic organisms. Some chronic cases go on for months or years in spite of treatment.

Treatment. All the ragged epithelium at the undermined edge should be clipped off. If there is excessive oozing of serum the most effective treatment is dusting with tannic acid. Local antiseptic baths with 1 in 5000 acriflavine lotion or dressing with hypertonic saline control the spread effectively. Bland ointments like borovaseline or plain zinc ointment should be applied at night. Internally, tonics with iron, arsenic and quinine in combination, or calcium lactate with parathyroid, act well. Vaccine therapy is recommended and is usually followed by marked improvement. Prophylaxis in the way of protection from injuries is very important.

Inflammatory Diseases of Unknown Toxic Origin

PITYRIASIS ROSEA. The lesions are of acute onset and characterised by fairly numerous pink or reddish scaly patches of various sizes and shapes with a slightly raised border and yellowish coloured centre. An attack may be heralded by slight fever and malaise with hard shotty enlargement of the submaxillary or inguinal glands, but other constitutional symptoms are absent. In quite a large number of cases prodromal symptoms do not appear at all. Individual lesions usually begin as small red papules on the back or the front of the chest and lower abdomen in the region of the waist line; these papules enlarge fairly rapidly and develop into rounded, oval or irregular maculo-papules, sometimes of considerable size. Contiguous lesions often coalesce into

segmental or gyrate lesions covered with fine bran-like scales. The eruption is asymmetrical and may be limited only to the trunk but the upper arms and thighs are also involved in a large number of cases. The face, palms and soles always escape. A few cases complain of a good deal of itching especially when they perspire, but subjective symptoms are generally absent and the general health remains good. The total duration of an attack is from 3 to 6 weeks and relapses are uncommon. In exceptional cases the disease may be prolonged to 2 or 3 months and each crop of eruptions generally follows on the heels of the previous healing ones. Spontaneous recovery takes place in majority of cases, the redness subsides, the raised margin sheds a fair amount of scales and soon becomes level with the general surface of the skin. There are no after-complications. The ætiology is not definitely understood but there are good grounds to assume that this disease is caused by a filter-passing virus. A small percentage of cases develops acid dyspepsia soon after recovery.

Treatment. *Local.* The patient should receive soothing ointments such as ichthyol ointment $\frac{1}{2}$ to 1 dr. to an ounce, or 2 per cent. ung. acid salicylic after a warm bath in 1 in 10,000 Condy's fluid. When there is a good deal of irritation, salicylic acid ointment may be combined with menthol and carbolic acid—5 gr. of each to every ounce.

Internal. Salicin in doses of 10 gr. twice daily and gradually increasing to 20 gr. per dose often aborts an attack. Hydrag. cum creta 1 gr. combined with pulv. ipecac 1 gr. is also of value. Ichthyol may be given internally with good results.

LICHEN PLANUS: Primary. The lesion is characterised by dry, shiny, purplish or violet-coloured papular eruptions, arranged in groups with a linear or annular distribution and affecting mostly the flexor aspects of the limbs, the trunk, face and neck. The mucous membranes of the mouth, vulva and the glans penis are also involved although the typical lesions are not often seen in these situations. Each papule is polygonal in shape and, occurring on the normal lines of cleavage of the skin, exaggerates the harshness of the texture so that a group of papules seem to form mosaic patterns on a deeply furrowed skin. The disease is sometimes acute in onset with slight constitutional symptoms and affects large areas on the thighs, forearms, lower portion of the back and abdomen. In severe cases the affected skin becomes diffusely red and cedematous but very soon assumes a violet or lilac colour. Small herald spots, few in number, may appear several weeks ahead either on the limbs or on the buccal mucous membrane. Spontaneous recovery may take place after a few months leaving the skin deeply hyper-pigmented or the disease may progress and affect other parts of the body. Occasionally atrophy of the affected areas is met with. A few patches very frequently persist as the so-called chronic variety particularly on the shin areas. The lesions are irritable.

The chronic type is far commoner than the acute and shows periodic exacerbations during which new spots appear and spread although the older lesions remain localised on the parts already affected. After persisting for several months or even years spontaneous involution may take place. A few cases are progressive in nature so that the lesions become hypertrophic. Intense itching is the most outstanding subjective symptom although all the patches are not equally irritable. Clinically, the hypertrophic or verrucous type may show linear distribution along scratch marks—*lichen planus linearis*. The affected skin may be atrophic so that the lesion closely resembles morphæa—*lichen planus atrophicus*. The skin may be intensely red and congested—*lichen planus erythematosus*, or show bullous formations—*lichen planus bullosus* and *multiforme*. In very rare instances hæmorrhage occurs in the skin—*lichen planus hæmorrhagicus*. The patches extend by coalescence of the papules. The aetiology of the disease is unknown. Acute onset sometimes follows nervous shock or excitement. Focal infection of the teeth and tonsils play a very important part and a certain percentage of cases shew sensitiveness to pollens, animal emanations and food proteins without any other definite evidence of an allergic condition. The trend of recent work points to the disease being caused by a filter-passing virus. The disease is most frequent during active adult life, but children are not totally immune. The changes in the skin consist of a sharply defined infiltration of the papillary and subpapillary layer with connective tissue cells extending as far down as the region of the coil glands. The papillæ are enlarged and œdematous and the papillary capillaries dilated. The horny layer is thickened and the rete shows a certain amount of hypertrophic changes.

Treatment. *General.* The patient should be kept on good nourishing and plainly cooked food and encouraged to lead a hygienic outdoor life as far as possible. All sources of mental worry and anxiety should be carefully avoided. The bowels and kidneys require attention as elimination through these channels is of importance. Mild aperients and alkaline citrates may be used in almost every case with good results.* A thorough investigation into the presence of septic foci in the teeth, tonsils, nasal sinuses or the bowels should be undertaken where laboratory facilities are available. Correlated allergic conditions should be determined and the source eliminated.

Internal. Preparations of mercury, arsenic or bismuth give the best results. The bichloride or biniodide of mercury may be given intramuscularly in 1/12 to 1/8 gr. doses suspended in olive oil. The patient receives one injection every day for 12 consecutive days with good results especially in acute cases, chronic cases often require two or three courses of injections at 6 or 8 weeks' intervals, all precautions being duly taken against the toxic cumulative effects of mercurial salts. Oral administration of liq. hydrarg. perchlor. in $\frac{1}{4}$ to 2 dr. doses twice daily is also of value. Arsenic in the form

of soamin injections biweekly or Neosalvarsan weekly often give very satisfactory results. Bismuth in the form of oily suspension of the metal or as bismuth salicylate solution in 2 to 3 gr. doses, given intramuscularly, are also useful.

Local. The acute cases require soothing antipruritic applications, e.g., liniment calamine with 3 to 5 min of phenol added to each ounce, or ichthyol lotion 10 to 20 per cent. Chronic hypertrophic verrucose types should be first canterised with 5 to 10 per cent solution of liquor potassi followed by application of 5 per cent salicylic acid ointment. Chrysarobin ointment can also be used. Lichen paint of the School Pharmacopœia offers a good combination of antipruritic and keratolytic agent which is painted on with a brush night and morning. Raw coal tar is also of value. An efficient combination for chronic hypertrophied lesions is as follows:—Menthol 1½ dr., thymol 2 dr., chloral hydrate 1 dr., chloroform and oil of eucalyptus 2 oz., oil gaultheriæ 4 dr., alcohol up to 8 oz. Lesions on the buccal or vulval mucous membranes are best treated with 5 per cent lactic acid or 0.5 per cent. chromic acid. Ultraviolet therapy may be used with advantage to relieve the itching of the skin. X-ray treatment has been recommended in fractional doses at weekly intervals and complete involution usually occurs in about two months' time.

Secondary lichen. It occurs at sites of old irritative lesions of the skin such as ringworm, seborrhæic and chronic allergic dermatitis. The condition may sometimes be brought about or exaggerated by too frequent use of strong irritant drugs and keratolytic agents which exert a stimulating effect on the rete accompanied by inflammatory vascular changes in the superficial layer of the corium. Treatment consists of removing the cause of irritation and use of milder keratolytic agents such as salicylic acid ointment 15 to 20 gr. to an ounce, to which may be added liq. picis carbonis ½ dr. and menthol 5 to 10 gr. Chronic cases with obstinate patches require X-ray treatment.

LICHEN NITIDUS. It is characterised by shiny, flat, flesh- or pink-coloured papules which are always discrete and slowly progressive in nature and produce no subjective symptoms. The commonest site of occurrence is the genitals although the breasts, thighs, arms and the lower abdomen may also be affected. The lesions involve the mouths of the pilo-sebaceous glands and are sometimes slightly scaly. Spread of the disease may be arrested for some time and spontaneous recovery is not very uncommon. The disease itself is often overlooked because of the absence of irritation which distinguishes this condition from lichen planus. The ætiology is unknown; some authorities believe that there is some relationship to tuberculosis.

Treatment. It is rather unsatisfactory. Local treatment with an ointment containing resorcin and salicylic acid (20 gr. of each in an ounce

of lanolin base) gives the best results when continued for some time. Internally iodine in gradually increasing doses has proved to be of some value. Stubborn cases should receive a trial with intravenous injections of gold sodium thiosulphate.

PSORIASIS. It is a chronic recurrent inflammatory disease characterised by circumscribed patches of erythematous lesions with dry silvery scaling surface. It generally affects the scalp, the ears, the extensor aspects of the extremities and the sacral region. The diagnostic features of the disease are the presence of micaceous, sometimes laminated, scales which are loose at the periphery and more or less firmly adherent at the centre of a patch; when these scales are removed the underlying skin is found to be markedly erythematous with points of bleeding from the tips of the papillæ. The onset is usually insidious beginning in the scalp where it is often diagnosed as dandruff in the earlier stage. Initial lesions may appear at the common sites of predilection or on any other part of the body as small guttate erythematous papules covered with fine silvery scales; the face, palms and soles generally escape. Spread of the disease is generally slow, the individual lesions enlarge by peripheral extension, and coalescence of contiguous patches often gives rise to gyrate patterns. Involution occurs in the centre of the patches and the edges become thick and tough owing to accumulation of scales. Acute exanthematic onset with appearance of numerous guttate lesions all over the body has been noticed in a few rare instances. The course of the disease is very inconstant. Individual lesions may remain localised and stationary for months with periods of improvement especially during the changes of the season. Spontaneous recovery at one place may be followed by appearance of fresh lesions at other parts of the body; there may be complete freedom from the disease for some years after which recurrence at the old sites or in an acute form may be ushered in without any warning. The general health is not affected although chronicity and recurrence is the rule; psoriasis does not induce alopecia. On the fingers and toes heaped up crusts accumulate beneath the nails and give rise to deformities such as grooving, discolouration and cracking of the free edge. Lesions in the axillæ, submammary folds, pubis, groins and gluteal folds often become extensively erythematous and sodden owing to perspiration and friction of clothes macerating the skin. Burning and itching renders the diagnosis difficult in such cases especially on dark coloured skin. Extensive generalised affection of the whole body is not very uncommon. The face, palms and soles may shew a few guttate lesions only in the acute exanthematic form of the disease but the condition should always be distinguished from syphilis which is far commoner than acute psoriasis. The disease is seen mostly in adults, affecting males more than females. Several clinical varieties have been described, *psoriasis guttata* in which the lesions resemble discrete drops; *psoriasis follicularis* in

which the lesions are situated at the mouths of the sebaceous and sweat glands; *psoriasis nummularis* in which the lesions are coin-shaped; *psoriasis osteacea* in which the scales are so thick and tough that they resemble the outside of an oyster shell. Other varieties such as *psoriasis gyrata*, *psoriasis discoides*, *psoriasis rupioides*, etc., have been described.

The aetiology is unknown although the parasitic theory has the largest number of supporters. The causative organism is considered to be a filtrable virus. There is good deal of hyperkeratosis and thickening of the rete with perivascular and perifollicular infiltration, the interpapillary vessels showing marked dilatation.

Treatment. General. Although psoriasis is generally a disease of the so-called healthy subjects, attention should be paid to diet and proper elimination and adoption of general hygienic measures is also of importance. A plainly cooked mixed diet, which is easily digested, is recommended; the patient should be encouraged to drink plenty of fluids and plain water to flush the kidneys. Fat-free diet has been recommended by many authors. Constipation, when present, should be treated with mild aperients and liquid paraffin; moderate exercise in the open air is helpful but vigorous exertions of any kind which induce a good deal of sweating should be avoided. Attempts should also be made to relieve mental worry as much as possible. A laboratory investigation for latent foci of infection should be undertaken wherever possible.

Local. The most effective local remedies are chrysarobin, salicylic acid and coal or wood tar. The scales are first removed by alkaline baths or soft soap and each individual patch is scrubbed with a piece of soft pumice stone till the papillæ of the skin are exposed as indicated by small bleeding points in the patch under treatment. Ung. chrysarobin (10 to 20 gr. to an ounce of lanolin), is applied and allowed to act for 4 to 6 hours. The centre of the lesion becomes white and anaemic and an erythematous reaction appears around the patch. Chrysarobin ointment is now removed with olive oil and some bland ointment (e.g., Lassar's paste or ung. borovaseline) applied on the treated patches. The treatment can be repeated the next day if there is no severe inflammatory reaction. Sensitive subjects may shew chrysarobin dermatitis which requires calamine lotion or other cooling preparations locally. In the scalp the hair is clipped short and a stronger ointment, containing 40 gr. of chrysarobin to an ounce, can be used. The patient should be warned not to touch his eyes while the ointment is on the scalp lest severe conjunctivitis set in. Chrysarobin can also be conveniently used as a paint dissolved in traumaticin (chrysarobin 10 gr., gutta percha 1 dr., chloroform 1 oz.) and thus save soiling of clothes and linen which stain permanently purplish black. This can also be attained by using a 2 per cent. alcoholic solution of chrysarobin on the lesions and subsequently painting with collodion. A very useful chrysarobin derivative is now available under the commercial name cynnolin; this is used as a

paint dissolved in chloroform or pure acetone in strength of 2 to 4 gr. to an ounce. It does not stain linen. Extensive areas of the skin should not be treated at one time with chrysarobin as absorption of the drug may cause acute nephritis. The urine should be examined frequently even when a patient is receiving chrysarobin applications over small areas but for a fairly long time. Salicylic acid is best used as an ointment in strength of 20 to 120 gr. in an ounce of lanolin or vaseline and can be combined with 5 to 50 per cent. crude coal tar. Better results are obtained when local applications are used with a certain amount of friction after softening and removing the scales with soft soap or alkaline baths. Coal or wood tar can be used pure but it is preferably used as a 10 to 15 per cent. ointment in a lanoline base. It can also be used in combination with salicylic acid; Ung. picis cum salicylic of the School Pharmacopoeia is a very useful preparation. All strong keratolytic drugs should be withheld whenever there is any sign of secondary irritation and cooling preparations like calamine lotion or plain olive oil should be applied instead. For psoriasis involving the entire scalp, lotions or pomades containing 10 per cent. resorcin and 5 per cent. salicylic acid are recommended for use at night. Psoriasis of the nails is very difficult to treat owing to the hard nail matrix preventing the remedial preparations from reaching the site of the lesion. The nail is first softened with caustic soda solution—Fehling's solution No. 2 is the best—and paints containing 1 to 5 per cent. chrysarobin in colloidion are used afterwards. X-ray exposures are of benefit but requires prolonged treatment which is not unaccompanied with the risk of X-ray dermatitis. Ultra-violet therapy has been recommended and is of benefit in acute exanthematic types in bringing down the inflammation. Its value in chronic cases is doubtful but general irradiation sometimes induces rapid involution. Chronic inveterate patches can be treated with X-rays but on the scalp the risk of permanent alopecia has to be borne in mind.

Internal. Salicin in gradually increasing doses acts beneficially in a large number of cases. Commencing from an initial dose of 10 gr. twice daily, the quantity is increased by 10 gr. every week till 30 gr. is reached. The maximum dose is kept up for three weeks. Other intestinal antiseptics, *e.g.*, liq. hydrarg. perchlor, zinc sulpho-carbolas, etc., have been used without any special advantage. Preparations of arsenic have also been recommended and can be administered either in the form of Fowler's solution or Donovan's solution. It is necessary to keep up the maximum dose for about six weeks and all precautions against the cumulative effects of the drug should be taken during the course of treatment. Cacodylates and arselyn may also be used by injection. The use of an autolysate prepared from the scales and diseased tissue has given encouraging results, but the best results are obtained when this is combined with a thorough local treatment in experienced hands. The removal of scales and scrubbing with pumice

stone followed up with application of chrysarobin or cignolin has effected the largest number of cures at the Carmichael Hospital for Tropical Diseases. Relapses, however, do occur and at the present state of our knowledge, there are no means of preventing them.

Inflammatory Diseases Characterised by Multiple Bullous Lesions of the Skin

EPIDERMOLYSIS BULLOSA. It is a rare hereditary condition in which blisters of varying size form on the skin as the result of trivial injuries or friction. In the majority of instances the disease is noticed in early infancy, the lesions appearing mostly on the back over the bony prominences or over the napkin area. Individual lesions are generally filled with clear serum but may, in rare instances, contain blood. The blisters rupture within a day or two of their appearance and heal fairly rapidly provided there is no secondary infection of the raw surface with pyogenic cocci. There are practically no residual scars on healing but the affected areas may become slightly depigmented. Repeated attacks may occur at the same site, and when the fingers and toes are thus affected, the growth of the nails is arrested. Deeper structures are sometimes involved especially when there is secondary infection of the ruptured vesicles and thus lead to contractures and other deformities. The disease has been known to have made its first appearance during young adolescence and has been described as the acquired variety. The aetiology is unknown but is assumed to be a defective development of the cementing fibrils which fix the epidermis to the subjacent tissues. The entire epidermis is lifted up in the formation of the blisters and there is slight dilatation of the papillary and sub-papillary vessels. The general health is in no way affected except in cases of extensive secondary infections. Subjective symptoms are conspicuous by their absence.

Treatment. The treatment is very unsatisfactory and protection from injuries even of a trifling nature should be undertaken rigorously. The blisters should be punctured aseptically and dressed dry with equal parts of zinc oxide, starch and boric acid. Calcium lactate with parathyroid in suitable doses is worthy of a trial. Where the affected child is born of a consanguineous marriage, blood transfusion from a person outside the family has been recommended. Spontaneous recovery with attainment of puberty is not very uncommon.

PEMPHIGUS. An acute or chronic inflammatory disease characterised by sudden occurrence of successive crops of bullæ on an apparently normal skin and accompanied with constitutional symptoms of varying severity. The mucous membrane of the mouth and entire gastro-intestinal tract as well as the conjunctivæ become ulcerated in the acute form of the disease which often terminates fatally from

toxæmia and exhaustion. The ætiology is not definitely known but a bacterial infection of some kind probably plays a very important part in the causation of the disease.

Clinical varieties. (1) Acute—malignant and benign; (2) Chronic—*pemphigus vulgaris*, *pemphigus follicaceus* and *pemphigus vegetans*.

Pemphigus acutus malignus. This is a disease most commonly seen amongst butchers and dealers in animal carcasses and generally commences from some injuries on the exposed parts of the body. The onset is accompanied with severe constitutional symptoms like fever, vomiting and prostration. Blebs of varying size appear on the limbs, body, face, scalp and buccal mucous membrane in successive crops; contiguous vesicles coalesce to form large blisters which may be as much as 10 cm. in diameter. The contents are generally serous but may become hæmorrhagic in very acute cases. The blisters soon rupture and leave raw sanguineous weeping surfaces which tend to spread progressively at the margins and shew no tendency to heal. Masses of detached epidermis and oozing blood-stained serum undergo decomposition and give rise to a very offensive odour. There is no itching or irritation but the affected areas are very painful which, together with joint pains, renders the patients immobile. Extensive ulcers form in the mouth, trachea and the whole of the gastro-intestinal tract, the conjunctivæ also become ulcerated, toxæmia deepens and the case terminates fatally from the effects of toxæmia, inanition and exhaustion within two or three weeks. Intercurrent diseases like pneumonia or cardio-renal failure very often hasten the end. In a few cases yellowish crusts form on the ruptured vesicles, the lesions cease to spread and recovery takes place only to pass into the chronic form (*pemphigus vulgaris*) of the disease.

Pemphigus acutus benignus. The constitutional symptoms are less severe and ulceration of the mucous surfaces is absent. Ruptured vesicles are soon covered with yellowish crusts and heal spontaneously leaving hyperpigmented scars. Some authorities classify this form under a separate heading with bullous impetigo. The disease is sometimes seen in children following vaccination against small-pox.

Pemphigus (chronicus) vulgaris. It is commonly seen in debilitated subjects beyond middle age and affects the face, mouth, neck or the genitals. The lesions may however appear on any part of the body and become generalised in distribution. As a rule, crops of vesicles appear in one part of the body and after persisting for some time disappear completely, leaving the patient almost free for more or less long periods of time. The first few attacks may be mild but the constitutional symptoms and extent of the disease become more and more severe with each recurrence. The mucous membrane of the mouth, throat, etc., are ulcerated and the patient develops the toxæmic prostrated appearance of pemphigus acutus malignus prior to a fatal termination in the course of a few months. The contents of the vesicles are at first serous but later becomes sero-sanguineous or sero-purulent. Death from intercurrent

pneumonia or cardiac and renal failure is more common in this type of the disease.

Pemphigus foliaceus. A rare and grave type of chronic pemphigus in which the bullæ are flaccid and imperfectly formed with a tendency to generalised exfoliation of the skin. There is no cohesion of the epidermis with the deeper layers so that the cuticle can be easily removed by friction or pinching (Nikolsky's sign). The blebs develop rapidly and involve almost the entire surface of the body; the contents, which are purulent from the very beginning, are set free by rupture of the vesicles soon after they are formed, the epidermis peels off leaving large raw surfaces covered with sero-purulent fluid. Large, fairly thick and loosely adherent crusts form on the surface and the discharges accumulate underneath and undergo decomposition giving rise to a foul sickening odour. To the palpating finger the surface of the body feels as if the epidermis is floating on a bag of fluid. Mucous membranes of the mouth, throat and trachea become raw and ulcerated and the hair and nails may be lost. Subjective symptoms are trifling or absent but constitutional symptoms of a mild degree persist throughout the course of the disease. Periods of quiescence follow exacerbation but the condition of the skin never clears up completely. The disease may be prolonged to several months and a fatal termination from intercurrent diseases is the rule. *Pemphigus foliaceus* is believed by some dermatologists to be due to secondary infection of the vesicles of *pemphigus vulgaris* with the pyocyanous bacillus (*Pseudomonas pyocyanea*).

Pemphigus vegetans. It generally commences as a bullous lesion on the mucous membrane of the mouth, throat and lips but as the vesicles rupture very soon after their appearance physical examination reveals only the raw moist bases. Blisters soon begin to appear on the nose, genitals, axillæ, groin, and the scalp and soon rupture. The raw bases instead of healing up become covered with papillomatous exuberant vegetations which are capped by crusts and exude a thick sero-purulent fluid of offensive odour. The subjective symptoms are slight and there are fairly long periods of intermission in the course of the disease, during which marked improvement is noticed without a complete cure. Constitutional symptoms are absent in the earlier stages but later on fever and nephritis set in as complications. The lesions in the mouth are very troublesome and hinder intake of nourishment. The patient becomes very susceptible to pneumonia and bacillary dysentery, either of which carries him away.

Treatment. *Acute cases.* The patient should be put to bed on a water or air mattress preferably, and his general health should be well looked after. The mouth should be gargled frequently with Condy's fluid or dilute B. C. lotion and painted with boroglycerin. A bath in 1 in 10,000 acridavin or weak Condy's lotion once a day is very helpful in keeping the skin clean and preventing secondary infection. The food should be bland, non-irritating and concentrated and given in small

quantities at frequent intervals. Internally, tonics particularly cod-liver oil, arsenic, iron and quinine are of value; of these, arsenic has been known to exert a curative effect in a few cases. It can be administered by the mouth as Fowler's solution or given intravenously as one of the arsphenamine preparations. Subcutaneous injections of coagulin are worthy of trial. Recently, Bayer 205 has been reported to have curative effect in some cases but its action on the kidneys should be carefully watched and the urine examined every day for presence of albumin. Locally, liniment of calamine is soothing. Continuous application of large quantities of plain dusting powder is also helpful. Extensive denuded areas should be kept moist with lint soaked in 1 in 5,000 acriflavin lotion.

For *pemphigus vulgaris* a conservative line of treatment yields the best results. Autogenous vaccines prepared from a culture of the contents of the vesicles have beneficial effects in checking recurrences. *Pemphigus foliaceus* requires frequent antiseptic baths and local application of dusting powder along with general tonics and cod-liver oil internally. Autogenous pyocyaneus vaccine is of considerable value. *Pemphigus vegetans* is treated on the same lines and auto-crotherapy has been found successful in a few cases.

DERMATITIS HERPETIFORMIS. It is a chronic, irritative, relapsing, inflammatory disease in which erythematous, papular, bullous or pustular lesions appear suddenly on the surface of the body and which tend to spread by peripheral extension. There are very mild constitutional symptoms which very often escape notice of the patient. The vesicles are very tough and do not rupture except through trauma and there is a tendency towards arrangement in groups. The disease has a varying clinical character but intractable and severe itching and burning is almost invariably present. An individual case may show erythematous, papular, bullous and pustular lesions all at the same time except in children who generally show the bullous and vesicular types of lesions. The sites of predilection are the posterior folds of the axillæ, the buttocks, abdomen, the forearms and the face. The lesions are very roughly symmetrical and the mucous membranes may be involved in very acute cases. Axillary, epitrochlear and inguinal glands become enlarged and inflamed as the result of secondary infection of the vesicles after they are ruptured. No age is exempted from an attack but the disease is more common amongst adult males in poor condition of health and nervous system. The disease may be prolonged to several weeks or months with periods of exacerbation alternating with those of quiescence. The ætiology, although not definitely known, is very closely associated with chronic auto-intoxication; pregnancy has also been found to be a very potent factor in women. Eosinophilia and indicanuria point to the disease being of allergic origin. The seat of the lesions is in the corium; the papillæ are oedematous,

the papillary and sub-papillary vessels are dilated, there is fair amount of perivascular infiltration and the entire epidermis is lifted up in the formation of vesicles.

Treatment. The first essential is to determine and eliminate all sources of toxæmia and this involves a careful investigation into the presence of septic foci in the teeth, tonsils and bowels. Attention should also be paid to digestion and elimination through the bowels and kidneys, mild cathartics and diuretics being exhibited whenever necessary. A dermal test for sensitiveness towards food or epidermal proteins is of great value and a complete cure can sometimes be obtained by total omission of the offending article of food. Internally, arsenic in the form of Fowler's solution or liquor arsenicalis hydrochloridum give encouraging results and in severe cases soamin, tryparsamide or neo-arsphenamine may be tried intravenously. Salicylates in full doses have been recommended but their effects are rather uncertain. Non-specific protein therapy in the form of autogenous serum, T. A. B. vaccine or milk sometimes yields very good results. Locally, alkaline, sulphuretted or bran baths have a soothing effect. The affected areas should be wiped dry without friction on emerging from the bath and a thick layer of calamine lotion containing 0.5 per cent. of carbolic acid and 5 to 20 per cent. of liquor carbonis detergens applied on lint. In severely irritable cases relief is often obtained by incising the vesicles and letting the contents out. Areas of excoriation should be treated with weak antiseptic ointments of which a 1 per cent. ammoniated mercury is by far the best. Bromides, luminal and other hypnotics are used when the intractable itching causes insomnia and consequent exhaustion.

Bullous Lesions caused by Filtrable Virus

HERPES SIMPLEX. The lesions consist of one or more groups of vesicles on erythematous and slightly oedematous bases and are always of acute onset. The commonest sites of predilection are the face and genital regions although the buttocks, arms and legs are sometimes affected. On the face, the lips, the nose, the ears and the cheeks are mostly involved and in the genital area the lesions appear on the prepuce, glans, sulcus, labia, mons veneris, clitoris and occasionally the urethra and cervix. The mucous membranes are hardly ever affected except on very rare occasions; there is slight fever and malaise when the vesicles appear in the mouth. The site may be irritable or there may be a feeling of pain and burning for a day or two before the actual appearance of the eruption. Other subjective symptoms and constitutional disturbances are generally absent. Herpes simplex very often accompanies pneumonia, influenza, meningococcal meningitis and malaria and shows a certain amount of familial tendency in its occurrence. Some subjects seem to have a predisposition and suffer with repeated attacks of herpes in approximately the same situation. Such recurrences may

follow intercourse, menstruation and intake of alcohol, spices, etc. The contents of the vesicles are at first serous but become sero-purulent in a couple of days or so. The walls of the vesicles are rather tough so that spontaneous early rupture does not occur. Involution sets in about a week after the appearance of the vesicles, some of which rupture and heal by formation of yellowish crusts while others get dry and drop off in about a fortnight's time. There is no residual scarring except when there is secondary suppurative infection. The cause of the disease is a filtrable virus of low virulence and having a saprophytic existence on the mucous membranes under healthy conditions.

Treatment. All possible sources of reflex irritation should be carefully looked for and removed. Locally, in the eruptive stage, a cold compress with 2 per cent. alum acetate solution is very useful. Painting the area with spirits of camphor and alcohol followed by dusting freely with zinc and starch dusting powder or powdered alum relieves the pain and burning. A thick coating of surgical collodion which is renewed every day is of value in preventing rupture and secondary infection of the vesicles. Lesions at the angles of the mouth can be touched up with a caustic pencil and dressed dry with talcum powder. In the genital region especially on the apposing mucous surfaces of the vulva, strict cleanliness is essential. The area should be swabbed with hydrogen peroxide and dusted with 5 per cent. aristol dusting powder (aristol 20 gr., zinc oxide and starch 4 oz. of each) three times a day. Recurrent cases require investigation into presence of focal sepsis in the teeth, tonsils, upper respiratory passages, bowels or pelvis.

HERPES ZOSTER. The lesions consist of groups of vesicles on an erythematous base and occur along the distribution of the fibres of nerves originating from one or more posterior root ganglia. The onset is acute and fairly rapid and is in many cases heralded by malaise, fever and persistent neuralgic pain. The cause of the disease is a filtrable virus of the same category as chicken pox and people coming in close contact with a person affected with herpes zoster have been known to have developed chicken pox after an incubation period of fourteen to sixteen days. Individual lesions have the same character as *herpes simplex* but are more intense and extensive and large patches consisting of a dozen or more vesicles appear in successive crops on the same side of the body. The contents of the vesicles are usually serous but may become sero-purulent owing to secondary infection; in rare instances the contents are hæmorrhagic. Lymph glands in the neighbourhood of the affected areas may be enlarged and tender. The average duration of the disease is about two to three weeks. A single attack confers immunity. On healing, the vesicles leave hyper-pigmented scars owing to involvement of the deeper layers of the epidermis. Certain drugs like arsenic and diseases of the cerebrospinal system notably

syphilis, tumours and traumatic injuries predispose to an attack. The site of appearance of herpes zoster may remain hyperæsthetic for months after an attack. The most serious sequel to herpes zoster of the face is affection of the cornea and the eyeball when the nasal branch of the ophthalmic division of the fifth nerve is involved.

Treatment. It is advisable to give the patient a good purge with calomel or blue pill followed by saline cathartics the next day. When the cornea is affected cold compresses with 2 per cent boric lotion are applied every 4 hours. The eye should be examined frequently by an ophthalmologist for serious corneal ulcers. The skin lesions are best treated with thick layers of talcum powder and cotton wool dressing. A hot water bag is very agreeable and relieves the neuralgic pain in mild cases. Aspirin, hypnotics of the barbituric acid series or even morphia may be necessary in severe cases. Extensive secondary pyogenic infection of the vesicles may require surgical interference and free drainage, the healing in such cases is generally uncomplicated. Mild galvanic currents and ultra-violet radiation sometimes give immediate relief; for severe pain pituitrin injection (0.5 c.cm.) is often useful.

Hæmorrhagic Lesions of the Skin

PURPURA. The disease is characterised by the occurrence of reddish or purplish eruptions due to extravasation of blood into the skin and mucous membranes. The lesions are flat and circumscribed and on a level with the general surface. Depending on the degree, extent and depth of occurrence these hæmorrhagic lesions are termed petechiæ, ecchymoses and hæmatomata. Purpura is either primary or secondary to other diseases.

Primary purpura. (1) *Purpura simplex.* The disease is of sudden onset without constitutional symptoms and is characterised by appearance of small petechiæ chiefly on the legs and mucous membrane of the mouth. The individual hæmorrhagic spots develop fully within two or three days and then fade gradually, the total duration of the disease being about a week or ten days. Successive crops may keep on appearing for months with slight fever and malaise, but the general health is not seriously impaired. Children and old debilitated people are usually affected but young adults sometimes, though rarely, suffer as well.

(2) *Henoch's purpura.* It is also found in children and is associated with vomiting, colic and diarrhoea of varying severity. The onset is sudden with joint pains but no rise of temperature and in severe cases the vomit and stool may contain blood. Hæmaturia may occur in a few instances and nephritis is a serious complication of the disease. Recurrent attacks do occur and a fatal termination is not very uncommon. The disease is probably allergic in origin and is due to sensitiveness towards some common articles of food.

(3) *Purpura rheumatica*. The petechiae are ushered in with fever, sore throat and multiple arthritis and the entire surface of the body and mucous membranes may be involved. *Purpura rheumatica* may be accompanied with urticarial, erythematous or bullous lesions of the skin similar to erythema multiforme or erythema nodosum. Pleurisy, pericarditis and endocarditis are serious complications. The disease may persist for several weeks or months but the average mild cases recover in two to three weeks. Recurrences do not occur as a rule.

(4) *Purpura hæmorrhagica or morbus maculosus*. In this type extensive hæmorrhages occur into the skin, the mucous membranes, the serous membrane and meninges. The onset is sudden and without warning and is manifested by fairly free bleeding from the gums, nose, stomach, bowels, uterus and urethra. These hæmorrhages may be of a severe nature and end fatally in the course of a week or so. Large areas of ecchymoses and hæmatomata appear on the skin, the entire buccal mucous membrane may be discoloured and hæmorrhagic. Young girls are more commonly affected and they show a marked fall in the platelet count. The disease may persist for months or years in a mild form with periods of intermission and improvement in bodily health.

Secondary purpura owe their origin to various causes of which the following are some of the more important :—

(i) Acute infectious diseases, *e.g.*, typhoid fever, cerebrospinal meningitis, plague, typhus, measles, small-pox and scarlet fever; (ii) Chronic nutritional disorders, *e.g.*, scurvy; (iii) Systemic disorders, *e.g.*, diseases of the heart, nephritis, pernicious anæmia, leukaemia, tuberculosis, and icterus gravis; (iv) Toxic purpura is caused by drugs like iodine and iodides, mercury, chloral hydrate, copaiba, quinine, ergot, belladonna, turpentine, salicylates. Snake venom also causes purpuric eruption; (v) Nervous purpura: severe fright or very strong emotions are sometimes followed by an acute onset. (vi) Mechanical pressure or gravity occasionally give rise to purpuric spots in susceptible individuals. Impediment to the circulation in the capillaries as occurs in embolism may cause a severe attack of purpura.

The important ætiological factor in the causation of purpura is the markedly increased permeability of the endothelial cells forming the capillary walls. Streptococcal toxins are mostly responsible for the onset of symptoms in purpura simplex and purpura rheumatica; in Henoch's purpura the allergic state which leads to extreme permeability of the capillaries of the skin and mucous membranes is the principal ætiological factor. The cause of purpura hæmorrhagica is not known.

Treatment. Except for the milder degrees of purpura simplex all cases of purpura should be treated as serious and the patient put at rest in bed with the first onset of signs and symptoms. Great care and gentleness should be used in handling the patient as slight pressure may lead to formation of ecchymoses or even hæmatomata. The foot end of the bed should be raised. The diet should be completely

changed and lightly cooked plain wholesome food given in small quantities at frequent intervals. All sources of focal sepsis should be carefully looked for and eliminated and a dermal sensitiveness test is always helpful in determining acquired sensitiveness towards common articles of food. Constipation, when present, should be treated with liquid paraffin or olive oil ; other laxatives are better avoided. For purpura rheumatica autogenous vaccines prepared from streptococci infecting the throat and tonsils or rheumatic phyllacogen is of great value. Attention should be concentrated on improving the tone of the capillary walls and diminishing their permeability and this can be attained by administration of calcium lactate 10 gr. combined with parathyroid 1/10 gr. twice daily by the mouth. Adrenalin is not a safe remedy owing to the fact that by raising the blood pressure it may lead to late hæmorrhage from the mucous membranes. In Henoch's purpura or morbus maculosus with extensive bleeding from mucous surfaces, normal horse serum 10 c.cm. or hæmoplastin 2 c.cm should be given intravenously as an emergency measure. Glucose should be given freely by the mouth or when necessary it can be given intravenously as a 12.5 per cent. solution in normal saline. Great care should be taken in using the ligature or digital pressure on the arm to make the median vein stand up prominently lest the area of pressure becomes hæmorrhagic. Acid sulphuric aromaticus in 15 to 30 min. doses has been recommended but this has no specific action except for its sedative effect. Blood transfusion and heteroserotherapy is sometimes curative for purpura hæmorrhagica. Vitamin D in large doses has a beneficial effect in most cases.

Treatment of secondary purpuras consists in removal of the underlying cause.

Inflammatory Diseases of Embolic Origin

ERYTHEMA NODOSUM. It is characterised by painful oval or rounded, raised, bright-pink coloured nodules surrounded by a halo of erythema and is ushered in with malaise, joint pains and rise of temperature. The evolution of these nodules is fairly rapid, attaining full development in six to twenty-four hours, and after persisting for about three weeks, they disappear spontaneously. The extensor aspects of the extremities are mostly involved, the lower more commonly than the upper. The lesions are usually symmetrical in distribution, few in number, tense to the feel and shiny in appearance; they are situated deep in the corium. Occasionally a few nodules of soft consistency are met with but they are always very painful and tender on pressure. Retrogression is heralded by change in colour from bright red to darkish red and purple; the consistency becomes soft and fluctuating almost simulating an abscess. These nodules rarely break down except when some secondary pyogenic infection is introduced accidentally. On healing, a dark or brownish stain is left for some time.

There is a certain amount of deep scarring which does not involve the epidermis. In exceptional cases, the nodules keep on appearing in crops and the total duration of the disease is prolonged to several months. The aetiological factor in a fair percentage of cases has been traced to streptococcal infection in the tonsils and teeth; the disease is a fairly common complication of rheumatic fever and has also been found in association with malignant endocarditis of non-rheumatic origin. There is marked dilatation of the papillary and sub-papillary plexus with oozing of serum accompanied by leucorrhoea and erythorrhoea. Some of the capillaries are embolised by streptococcal vegetations and there is aggregation of leucocytes around them.

Treatment. During an attack the patient should be kept at rest in bed; the bowels should be moved by suitable aperients whenever necessary and the kidneys flushed with drinks of plain water or other sweet drinks. Internally, an alkaline mixture containing 10 gr. of natural salicylate of soda with double the dose of the bicarbonate is given three times a day. Quinine in 5 to 10 gr. doses and salicin in 10 to 20 gr. doses, given twice daily, are also useful. Locally, 10 per cent. ichthyol ointment acts as a sedative, and this may be alternated with application of plain calamine or Goulard's lotion during the day. A thorough investigation into the presence of septic foci in the teeth and tonsils is of great importance in preventing a relapse which is not very rare. Autogenous streptococcal vaccine from these foci of infection is of proved curative value. Patients in run down or otherwise poor condition of health require iron arsenic and quinine tonics and cod-liver oil as an adjuvant to specific treatment.

LUPUS ERYTHEMATOSUS. The disease is characterised by the occurrence of pink, infiltrated plaques covered by adherent scales which tend to spread at the margin and heal in the centre with formation of atrophic scars and telangiectases. The lesions are quite superficial and do not ulcerate but are extremely persistent and slowly progressive in nature. When the scales are removed the follicles of the affected area appear dilated and some are filled with horny plugs. These epithelial plugs are usually firmly adherent to the under surface of the scales. Clinically, two types are met with, (i) the acute disseminated exanthematic type and (ii) the chronic circumscribed or localised type. Multiple lesions may appear in both types of case, the patches being of various configurations. Coalescence of neighbouring lesions often takes place at their extending periphery, thus involving extensive areas on the face, head and neck, hands, vulva and the perineum. The mucous membrane of the mouth is also commonly affected.

(i) **THE ACUTE DISSEMINATE TYPE.** The lesions may appear suddenly without prodroma and are accompanied by high fever and general constitutional disturbances. In a few instances the acute exacerbation may be superimposed upon the chronic circumscribed type.

No part of the body is exempt from affection although the palms and soles escape in the majority of cases. Individual lesions may be nodular or vesicular in character and in very severe cases hæmorrhagic. Crops of lesions appear at different parts of the body at the same time. Some patches heal up spontaneously while others develop into the circumscribed type of lesion. The buccal mucous membrane is almost always affected. Repeated attacks may ultimately lead to a fatal termination from pneumonia or pulmonary tuberculosis. This type of the disease is comparatively rare and causes practically no subjective symptoms. A few cases complain of a burning sensation.

(ii) **THE CHRONIC CIRCUMSCRIBED TYPE.** The onset is insidious and is not accompanied with any symptoms. Characteristic lesions consist of well defined, dry, pink or reddish patches, varying in size from a pea to the size of the palm of the hand and are covered with greyish adherent scales. The sites of predilection are the flush areas of the cheeks and the bridge of the nose, the mastoid area, the lobes of the ears and the scalp and front of the chest. On the face the distribution is often symmetrical on both cheeks with a narrow strip-like lesion along the nose giving rise to the typical butterfly shaped patch. The skin is only slightly infiltrated and the inflammatory changes are practically confined to the edges where extension of the lesion takes place. Atrophic changes with depigmentation and scarring in the centre of a patch and telangiectasis or 'gun barrel blue' discoloration of the margin constitute the typical clinical picture. Occasionally the healed areas are deeply pigmented. The mucous membrane of the mouth is involved in about 25 per cent. of cases; the lips, eye-lids and tongue are also affected. Lesions of the mucous membrane may appear only as slight thickenings with abrasions or scaliness of the affected part. Thin atrophic scars are left on healing. On the scalp the patches are hairless, harsh, sclerosed and extremely irritable.

The course of the disease is somewhat erratic but slowly progressive. Spontaneous recovery occasionally takes place without any residual scarring, but recurrence is almost always the rule. The disease generally appears between the second and fourth decades of life and women are more often affected than men. The principal ætiological factor is septic embolism of the fine capillary twigs in the papillæ derived from latent foci in the teeth, tonsils or nasal sinuses.

Treatment. Acute cases are treated on general lines and each case has to be carefully investigated for latent focal sepsis especially in the teeth and tonsils. All metabolic defects or circulatory derangements should be corrected. Absolute rest and small fractional feeds of concentrated nutritious liquid diet are indicated when constitutional symptoms are severe. Elimination through the bowels and kidneys should receive attention. Locally, cooling soothing lotions are used as cold compress during the day and the affected parts are smeared with pure olive oil at night. A tepid sponging towards the evening often

induces restful sleep at night. Of the various local remedies calamine lotion and white lotion (sodium chloride 1 part, sodium bicarbonate 2 parts and boric acid 3 parts in 100 c.cm. of distilled water) give the best results.

The chronic circumscribed cases also merit a thorough investigation into latent septic foci which should be located and eradicated. General hygienic measures are of importance. The diet should not contain any hot spices or condiments and stimulating drinks, particularly alcohol, are forbidden. Exposure to bright strong sunlight or extremes of heat and cold are harmful.

Local. Acutely inflamed and oedematous spreading lesions should be treated with continuous wet dressing of calamine or white lotion till the inflammation has subsided. Individual patches are then painted with 5 to 20 per cent. alcoholic solution of salicylic acid or resorcin, morning and night, to induce exfoliation. Perchloride of mercury may be added in strength from 1 in 5000 to 1 in 2000. The application is discontinued if there is any sign of irritation. When the scales have come off the patches are painted with phenol or trichloroacetic acid. Freezing with carbon dioxide snow sometimes gives good results.

Ultra-violet radiation in strong doses of five to thirty minutes are useful for obstinate patches and marked improvement follows when the reactionary hyperæmic stage has subsided. Complete recovery may sometimes take place but exacerbation after a period of quiescence is more common. General radiation should be undertaken with great care, as a sub-erythema dose often causes dissemination. X-rays and radium therapy have been tried with occasional successful results but as the chronic character of the disease requires prolonged treatment, X-ray and radium dermatitis and burns are serious sequelæ.

Internal. Tonics with combination of iron, arsenic and quinine are of great help in stimulating the defence mechanism of the body. Calcium lactate in 10 gr. doses combined with 1/10 gr. of parathyroid are given twice daily for toning up the capillaries. Cod-liver oil and its preparations are indicated when the general health is poor. Focal sepsis has to be treated with suitable autogenous vaccines and other specific measures. Preparations of gold, e.g., sanocrysin, solganal A and B, and krysolgan have been used intravenously with varying success and of these krysolgan is more often used on account of the stability of the compound in solution. All due precautions are necessary in exhibiting gold products and frequent examination of the urine for the presence of albumin and free erythrocytes are essential. The initial dose of krysolgan is 0.0015 gr. and the maximum 0.075 gr.

Best results are obtained by adopting measures which combine general, local and so-called specific therapy and treatment has to be varied and adopted according to the nature, duration and situation of the lesions.

ALOPECIA AREATA. The disease is characterised by sudden and total loss of hair in patches and affects usually the scalp but may involve other hairy areas of the body namely the beard and moustache, eyebrows, pubis or the body. The affected area is round or oval in outline with a few loose hairs at the periphery and the skin is smooth and glossy. The hair is broken off flush with the scalp and when pulled out present an 'exclamation mark' appearance due to atrophy of the bulb. In extreme cases total baldness may supervene in a few days by steady falling of the hair in large bunches. Spontaneous recovery is heralded by growth of very light-coloured downy hair which are soon replaced by stronger and stouter hair. This second crop is at first very light-coloured or white but gradually changes to normal colour and texture. The improvement may be arrested at any stage resulting in permanent baldness or the patches of white hair may persist. Occasionally the disease continues indefinitely and is characterised by successive growths of weak short-lived hair.

The disease is of inflammatory origin and is due to septic embolism and toxic inflammatory changes in the blood vessels of the papillary portion of the corium. The most important focus of sepsis is in the teeth in the form of dental caries or apical abscesses. Streptococcal infection of the tonsils is also present in a fair number of cases. Endocrine and nervous imbalance are other important aetiological factors. The disease usually affects grown up children and young adults of both sexes; universal or total alopecia is more common in adult men.

Treatment. Every case requires investigation in the presence of sepsis in the teeth and tonsils which should be treated by extraction, operative measures and autovaccine therapy according to the merits of the case. All sources of mental worry and anxiety should be removed. Vascular tonics like calcium lactate 10 gr. with parathyroid 1/10 gr., general tonics and cod-liver oil are very useful. Hexamine in 10 gr. doses given over a fairly long period usually cuts short the duration of the disease. Endocrine glandular products are required for cases with evident defect or imbalance of the ductless glands. When mental or nervous factors are present sedatives and hypnotics are indicated.

Local. Stimulating applications are indicated of which 95 per cent. phenol gives most satisfactory results. It should be applied as a thin film and allowed to remain for about an hour. For treating patches on the eye-brows or the face it should be diluted with equal part of glycerine. An ointment containing pilocarpine nitrate 1 gr., betanaphthol 1 dr., lanolin 2 dr. to an ounce of vaseline is recommended; this should be applied with friction over the patches twice daily.

Disease Caused by Spasm of the Blood Vessels

RAYNAUD'S DISEASE. It is characterised by symmetrical acrocyanosis, asphyxia and gangrene of the soft tissues of the fingers, toes and sometimes the ear and nose. The attacks are paroxysmal in nature and the ischæmia is caused by spasmodic constriction of the arteries supplying the affected part. During the spasmodic phase the part becomes pale, cold and numb and later on blue. Return to normal conditions takes place during the earlier stages without any impediment to the circulation but after several attacks the affected areas remain persistently cyanosed and painful. Superficial necrosis sets in and a gangrene of the dry type may follow, causing spontaneous amputation of several digits.

The exact cause of the disease is unknown. The syndrome is produced by local sympathetic irritability causing at first intermittent and then almost continuous spasmodic constriction of the arteries. It is sometimes associated with scleroderma. Highly strung and neurotic types of young adults are affected, the women more often than men.

Treatment. In the early stages the treatment is palliative with hot baths, massage and high-frequency current combined with general tonics, calcium and cod-liver oil. Preparations of muscle extract yield very good results, which can be used both orally and intramuscularly. When gangrene sets in the treatment is purely surgical. Periarterial sympathectomy is followed by permanent cure.

Neuroses of the Skin

PRURITUS (Itching). It is more a symptom than a distinct clinical entity and accompanies various skin diseases of both external and internal origin. It may be defined as intractable irritation of the skin, usually of a spasmodic nature, without any evidence of dermatitis or other inflammatory lesions on the surface. As a rule, localised areas on the trunk or limbs are affected but involvement of the whole body is not very rare. Acute cases shew objective signs which are the results of scratching, namely, blotchy erythema, excoriation, blood crusts, fissures and wheals. In chronic cases of fairly long duration pigmentation and lichenification supervene as secondary changes in the skin. Every case of pruritus should be investigated thoroughly to determine the underlying cause of which the following are important:—(1) Systemic diseases like diabetes, carcinoma, leukaemia, arteriosclerosis, Bright's disease, Grave's disease, certain disorders of the nervous system, Mycosis fungoides. (2) Intoxications, *e.g.*, high blood icterus, faulty elimination and stasis in the bowels, fermentation and chronic dysentery. (3) Ingestion of certain foods, especially shell fish and tinned products. (4) Ingestion of certain drugs which are eliminated through the skin, *e.g.*, copaiba, arsenic, etc. The commonest external causes are:—

(1) Mechanical, such as harsh or woollen clothes, corsetry and tight lacing, stretching of the skin as in pregnancy, etc. (2) Chemical, *e.g.*, too frequent use of soap, aniline dyes used for colouring socks, stockings, and underlinen, chemical insecticides, etc. (3) Parasitic, *e.g.*, scabies, ringworm and seborrhoeic dermatitis.

Treatment. General. Removal of the cause is the first essential and in attaining this, every case has to be treated on its own merit. Co-operation of the patient is a very important factor and highly strung or neurotic subjects are sometimes extremely difficult to treat because the habit of scratching is kept up subconsciously. Administration of calomel in a 2 to 4 gr. dose at bed time followed by a saline cathartic the next morning is a good routine measure to adopt. A complete change of diet is also of value. Exhibition of sedatives may be required for relieving the irritation, especially when the patient is tired and exhausted for want of sleep at night. Bromides in full doses and barbituric acid derivatives can safely be given at bed-time to induce restful sleep. Harsh woollen clothes should be replaced by garments of soft silk or cotton and the room should be kept comfortably cool and well ventilated.

Local. A soothing bath containing bran, bicarbonate of soda or menthol is given twice daily. The temperature is kept at about 78° to 80° F. and cold water is gradually added till the temperature drops to about 55° to 60° F. A cold spray before emerging from the bath is advised. The skin should be dried by gently patting with a soft towel and dusting powder or antipruritic lotions applied liberally. Of the various anti-pruritic remedies phenol in a 2 to 5 per cent. lotion and menthol in 0.5 per cent. alcoholic solution give best results. Liq. carbonis detergens in 2 to 8 per cent. alcoholic solution is also of value. Cocaine can be used as an antipruritic remedy only when the patient is under careful and strict supervision. The use of phenol lotion even in a fairly weak solution over extensive areas for a long time may induce local gangrene and toxic effects from absorption of the drug. Generalised ultra-violet radiation sometimes brings immediate relief. Repeated exposures are necessary in the treatment of chronic cases and the abatement of symptoms is always gradual. Radium therapy has been advocated for localised and stubborn pruritus especially of the muco-cutaneous regions.

Chronic localised pruritus of the anus, vulva or scrotum may be due to external local or internal toxic causes. A thorough physical examination is always indicated to determine and eradicate external sources of irritation. Secondary changes like hyperkeratosis and lichenification set in early in the disease and the skin and the mucocutaneous junctions present a peculiar glazed appearance. The secondary changes are very often responsible for persistence of subjective symptoms.

TREATMENT. Before commencing local treatment the bowels should be opened well with suitable cathartics and the diet changed to plainly cooked, nutritious and wholesome foods. All kinds of tinned foods should

be completely stopped. Stimulating drinks, especially alcohol, are contra-indicated. The patient should be encouraged to drink fairly large quantities of plain water to keep the kidneys well flushed. External parasitic infections should be treated on specific lines and antipruritic lotions and ointments can be applied when occasion arises. Best results are obtained from X-ray therapy and it may be necessary to continue the exposures for some time before permanent cure is established.

PRURIGO. It is a chronic inflammatory disease characterised by the appearance of successive crops of small, flesh-coloured, extremely itchy papules with a predilection for the extensor aspect of the limbs and the lower abdomen. These papules become excoriated owing to the scratching and the skin between the papules is often xerotic or eczematoid. A large percentage of these cases shew dermographism. Lesions may occasionally appear on the trunk, face, forehead and the scalp but the skin of the groins and axillæ are always free. Cases very often commence as papular urticaria of early childhood and, instead of recovery, the clinical appearance changes to the characteristic lesions of prurigo which may then persist indefinitely. Secondary changes of the skin, e.g., excoriations, pustulation, lichenification, scarring and enlargement of superficial glands, especially of the groins, are usually present in well-established cases. The incessant irritation of the skin and slow intoxication give rise to nervous instability, secondary anaemia, loss of appetite, constipation and mental and moral impairment. The ætiology of the disease is not known but it is very closely related to the allergic group of inflammatory diseases with which it is often associated.

Clinically, three varieties have been described: (a) *Prurigo mitis* is a comparatively mild affection and the constitutional disturbances are not very marked. (b) *Prurigo ferox* is the severe form of the disease characterised by incessant scratching, constitutional disturbances and mental impairment. The disease is usually localised in certain areas although the whole body is sometimes affected. *Prurigo ferox* is a comparatively rare disease. (c) *Prurigo nodularis* is an extremely rare form of chronic inflammatory disease characterised by formation of nodular eruptions, chiefly on the lower legs, and constant intractable irritation which prevents the patient from taking rest by day or night. The onset is insidious and is sometimes associated with urticaria. Women are affected more often than men. Secondary changes in the skin are not very marked but the general health is always affected for want of proper sleep and rest. The ætiology is not known and unlike *prurigo mitis* and *prurigo ferox* the disease appears later in life.

Treatment. General. A thorough investigation into the presence of septic foci and other sources of auto-intoxication is essential. The diet should be changed radically and good nourishing food, plainly but agreeably cooked, is indicated. Tonics with combination of iron, arsenic,

quinine and strychnine are necessary in cases with a low condition of health. Thyroid extract in half grain doses twice daily can also be given for its tonic effect. General ultra-violet light baths are beneficial.

Local. Antipruritic lotions and ointments containing 1 to 2 per cent. of phenol and 2 to 3 per cent. of liquor carbonis detergens relieve the irritation to a great extent. Beta naphthol 2 per cent. with coal tar 10 per cent. in lanolin base is useful when secondary hyperkeratosis is present. Prurigo ferox responds quickly to X-ray therapy and radical cure may be established within two to four weeks, especially in children. In the case of adults a good many recur after complete freedom from symptoms for some months.

Prurigo nodularis calls for strong chrysarobin (2 to 5 per cent. in a lotion) and X-ray therapy for relief of symptoms. Freezing with carbon dioxide snow or complete excision of the nodules give satisfactory results although a few nodules may recur and require treatment for the second time. Phenol and liquor potassæ, 15 per cent. of each, dissolved in olive oil sometimes give immediate but temporary relief.

GRANULOMAS. These are solid areas of cellular infiltration of the pars reticularis of the corium induced by specific micro-organisms or their toxins and consist chiefly of endothelial cells. Granulomas are classified as follows:—

I. Those that pass through three distinct stages before the granulomatous lesions are fully developed, namely:—(a) Initial lesion followed by lymphatic permeation. (b) Invasion of the blood stream, septicæmia and production of cutaneous rashes. (c) Granulomatous stage with or without ulceration. Examples are syphilis, yaws and leprosy.

II. Those that shew two stages in their evolution, namely, (a) Initial lesion followed by lymphatic permeation and spread to the nearest lymph node. (b) Formation of granulomas along the lymphatics when further spread is obstructed by sclerosis and fibrosis. Examples are tuberculosis, blastomycosis and sporotrichosis. All these lesions break down and ulcerate.

III. Those with only one stage, namely the initial lesion at the site of implantation with both centripetal and centrifugal spread. Examples are actinomycosis, oriental sore, rhinoscleroma and infective granuloma.

In dermal leishmaniasis there is no initial lesion but the parasites are lodged in the peripheral vessels and give rise to leucodermic spots at first, the granulomatous nodules developing afterwards. The lesions hardly ever ulcerate.

Botriomycosis or granuloma pyogenicum is not a true granuloma but a condition of excessive growth of granulation tissue owing to the irritation of an infective organism, usually the staphylococcus.

Treatment. The treatment of different types of granulomas has been dealt with in various chapters.

DICTIONARY OF DISEASES AND TREATMENT

ACNE VULGARIS. See page 1158

ACTINOMYCOSIS. See page 1159

ACUTE ABDOMEN. It is an emergent condition where the question of immediate surgical operation will have to be seriously considered. In a few conditions, the treatment may be purely medical. There are extra-abdominal diseases such as acute pneumonia, especially in children, coronary thrombosis, the gastric crises of tabes, uræmia, Henoch's purpura and diabetes, which occasionally give rise to pain and vomiting simulating acute abdominal diseases. In such conditions as the inflammations of various kinds of the abdominal viscera and their appendages, namely, acute appendicitis, peritonitis, salpingitis, pancreatitis, cholecystitis, perforations of gastric, duodenal, stercoral and typhoid ulcers, hæmorrhages from ruptured ectopic gestations and ruptured blood cysts of the ovary, torsions of an ovarian cyst or of the gall bladder and lastly the different types of acute intestinal obstruction, the question of immediate operation is to be considered without unnecessary delay. The non-surgical acute abdominal conditions include the various types of colic such as the intestinal, renal, biliary or lead colic, acute constipation and such emergent conditions as pyelitis, Dietl's crises, abdominal influenza, typhoid and tuberculous peritonitis.

CERTAIN DIAGNOSTIC FEATURES OF ACUTE ABDOMINAL EMERGENCIES

Temperature. Usually the temperature is not high in acute abdomens, and it is quite unusual to find a temperature above 102°F., but children run higher temperatures than adults, while elderly people run lower temperatures than the middle aged; a temperature of 99° or 100°F., in an acute surgical abdomen, is the most usual condition. It is only in acute gall-bladder diseases and in inflammatory conditions that a high temperature is met with. A steadily rising pulse is a sign of grave prognostic importance. In acute abdominal catastrophes during the period of shock, the pulse is rapid and thready. A very sudden acute abdominal lesion may, therefore, give rise to thin, rapid pulse and a subnormal temperature in the beginning. After some time the pulse begins to rise and attains a normal count. This occurs in the reactionary stage and may give a misleading impression of improvement of the patient's condition.

Vomiting. This occurs in many of the acute illnesses and is particularly met with among children. Repeated vomiting with acute pain in the abdomen and a distinct pallor on the patient's face often suggest a

grave condition. The change of smell and colour of the ejected materials from the ordinary smell of food to a faecal odour usually indicates some form of obstruction of the bowel either paralytic or organic. Faecal vomiting is often a sign of impending death.

Pain. The site of origin, the nature and the mode of radiation of pain are important diagnostic features in acute abdomens. Inflammatory pain starts very gradually while the patient is resting and gets steadily worse in the course of a few hours; the patient lies still and never writhes about in bed. The pain in appendicitis, pancreatitis, etc., seems to start while the patient is in bed in the early hours of the morning. On the other hand, pain in acute obstruction or colics is of a gripping nature, and the patient often writhes about. A sudden onset of pain of great severity suggests perforation or acute strangulation of the gut.

EXTRA-ABDOMINAL CONDITIONS. Pneumonia. In many chest conditions such as early pneumonia or pluerisy, especially the diaphragmatic variety, the pain is acute and referred to the abdomen. Other signs of acute abdomen such as rigidity of the abdominal wall, vomiting, etc., may also be present but, as opposed to true acute abdominal cases, the temperature is high, the pulse-respiration ratio is characteristic and the rigidity is not a genuine one.

Uraemia. Uraemic cases simulate acute obstruction with symptoms of abdominal distension, pain and vomiting. Intense toxæmia also suggests the condition.

Coronary thrombosis and acute coronary embolism often simulate an acute abdomen with an acute pain in the upper part of the abdomen, a rapid pulse and vomiting ultimately leading to a state of collapse.

INTRA-ABDOMINAL CONDITIONS. Typhoid. The disease is essentially an abdominal one and sometimes presents signs and symptoms of acute appendicitis. Appendicitis when present is caused by bacillus typhosus associated with general enteritis. A true emergent condition supervenes only when a typhoid ulcer perforates necessitating immediate surgical intervention. In the so-called abdominal influenza the pain is of a colicky nature and not of an inflammatory type. Vomiting and distension of the abdomen are present but the temperature generally shoots high.

Colics. The pain of biliary and renal colics has particular sites of origin and definite distribution. The pain in biliary colic starts in the right hypochondrium, radiates towards the epigastrium, behind to the back and ultimately terminates near the shoulder blade. A biliary colic may settle down with morphia. In renal colic, the pain starts at the back near the renal angle under the last rib and radiates round and down to the front into the groin, testicle or thigh. Vomiting is more marked in biliary colic. Intestinal colic is often due to ingestion of indigestible materials and causes a violent gripping pain, which sometimes resembles an acute obstruction.

Genuine acute abdominal emergencies include cases of inflammation, obstruction, perforation and hæmorrhage.

Inflammation. These cases usually give rise to a slowly rising pulse and temperature, pain comes on gradually and an area of rigidity and tenderness develops over the inflamed viscus. Of the various inflammatory conditions, acute pancreatitis and appendicitis need a detailed description.

Acute pancreatitis. The pain here is even more acute than that of perforation and shock is invariably present. Prostration is marked from the onset, and the pulse is rapid, thin and feeble. Abdominal rigidity is always present especially in the upper part.

Acute appendicitis. The ætiological factors are still obscure. Undoubtedly it is a disease of civilization with its adequate supply of pure rich food of all descriptions. It may occur at any age, it is rare in the aged and most common in the 2nd, 3rd and 4th decades. Organisms such as *Bact. coli*, staphylococci, streptococci, *B. welchii*, tubercle bacilli and actinomycotic fungus have all been isolated from acute cases, occasionally in pure cultures, but usually the infection is mixed. Urgent gangrenous appendicitis is only seen amongst the meat-eating people and is twice as common in the male as in the female.

The pain in acute appendicitis starts as a general abdominal discomfort round the umbilicus, described by the patient as a stomach-ache and is usually of gradual onset and associated with general malaise. Nausea, retching or vomiting follow abdominal pain and vary in their intensity; patients usually vomit once or twice only. The temperature is usually 99-100°F., and if it is higher than 101°F., a careful examination for other causes should be made before diagnosing appendicitis.

The pain, varying in intensity and radiation, ultimately settles down in the right iliac fossa. The pain in acute appendicitis is made worse on walking or on extension of the thighs due to stretching of the psoas muscle. A sudden cessation of pain and a feeling of well-being or marked improvement suggests gangrene or perforation with the relief of tension. If the appendix is lying on the bladder, it may give rise to frequent or painful micturition. A retrocæcal appendix may be close to the gall-bladder and so mimic acute cholecystitis. The bowels are usually constipated. The results of an enema are nil and this indicates a reflex inhibition of the bowel activity caused by the presence of inflammation in the lower abdomen. Acute appendicular obstruction shows a different clinical picture. It is characterised by the sudden onset of severe, colicky, general abdominal pains, sometimes doubling up its victims and causing them to roll about. The restlessness is of diagnostic significance; it indicates a mechanical pain, whereas inflammatory pain usually immobilises its victims; they lie still on their back, sometimes on their side with the legs flexed; the tongue is furred and moist, and the breath offensive.

Hyperæsthesia is tested for with a pencil-point, stroking the abdomen in longitudinal and transverse directions. In 40 to 50 per cent. of cases it is present in the right iliac fossa and it is said to be an indication of an unruptured appendix. The right iliac fossa is usually painful and tender and shows varying degrees of muscle tension or rigidity centred half way between the umbilicus and the right anterior superior iliac spine. The rigidity in the right iliac fossa is the response of the parietes to the close underlying inflammation. Rectal examination should never be omitted. Anything from a slight tenderness in the right iliac fossa to appendicular masses like tense collars about the rectum or bulging abscesses may be discovered. The complete series of changes starting with appendicular obstruction to gross general peritonitis may occur within four hours.

In one, two or three days, the symptoms may pass on to those of general peritonitis or may completely subside. If resolution does not take place, a local abscess is formed with a tumour in the right iliac fossa, in the pelvis or in the loin. The slight pyrexia persists, constipation will continue or diarrhœa may occur. In abscess formation, after the fifth or sixth day, the pain may become more severe as the tension in the abscess cavity increases, and according to its situation, it may track through the abdominal wall and open into the groin or it may burst into the rectum, vagina or general peritoneal cavity with disastrous results. A retrocæcal abscess may track up and form a subphrenic abscess later.

Obstruction. Intense griping pains and increasing vomiting are met with in these cases. Rigidity is usually absent and tenderness is more or less diffused all over the abdomen. There is marked visible peristalsis. The common causes of obstruction are strangulated hernia, volvulus and intussusception. Intussusception occurs usually in babies and has very characteristic symptoms. The acute catastrophies which occur in connection with abdominal diseases are in truth the acute terminations of chronic diseases and are rarely acute new diseases.

Perforation. The perforation of an ulcer in the stomach or duodenum is almost invariably preceded by the history of a chronic ulcer and that some exacerbation of symptoms may have been observed in a few preceeding days. The pain is sudden in onset and of acute burning type. The temperature is usually subnormal and the patient lies absolutely still with a thin rapid pulse. The abdominal parietes present a board-like rigidity and are intensely tender. Shock is never a symptom of perforation. It is a symptom of peritonitis which follows quickly upon leakage from the stomach or duodenum. Percussion yields a high-pitched tympanitic note, which is always suggestive of a mixture of gas and fluid in the abdominal cavity. Liver dullness may or may not be absent, but as a general rule it is diminished. In duodenal ulcer, the perforation is on the right hand side of the spine and the fluid runs down to the right iliac fossa which is painful tender

and rigid as in appendicitis. Perforations are also met with in cases of typhoid and dysenteric ulcers.

Hæmorrhage. This is seen in ruptured ectopic gestation. It occurs in the second or third month of pregnancy. There is a sudden onset of violent pain and collapse and the patient becomes pale and restless, the pulse runs up rapidly with all other signs of an internal hæmorrhage. There is no swelling, no rigidity but a diffuse tenderness is present all over the abdomen.

TREATMENT. A correct diagnosis of cases as far as possible with an immediate operation is required in these cases to ensure the safety of the patient. In some forms of acute abdominal diseases, the indications for urgent operation are clear and universally admitted. In perforations of all kinds, in ruptured ectopic gestation, and in the more acute forms of obstruction, such as volvulus, intussusception, and the various forms of internal strangulations by bands and apertures, operation at the shortest possible notice is clearly indicated. Opinions differ regarding the suitable time for operation in acute appendicitis. The statistics all over the world have proved conclusively that the mortality of cases treated by operative measures within the first 24 hours is practically nil, provided there are no complications. In children the axiom is, always to operate immediately and remove the appendix, irrespective of the duration of the disease and of the condition of the appendix. In case of acute appendicitis seen within the first 48 hours of the attack, it is generally agreed that the appendix should be removed. If cases are brought when symptoms have subsided, operation may be postponed till the quiescent stage. The treatment of intermediate cases varies. Cases showing improvement from day to day and from hour to hour should receive a constant watch. In such cases, the leucocyte count should be done twice a day, pulse registered every hour and the patient should be, if possible, under direct supervision of an expert surgeon. When these are not available, Ochsner and Sherren advocate Fowler's position, water and glucose by mouth followed by liquid diet if the temperature and pulse subside. If with such treatment, the leucocyte count shows steady increase or a sudden drop or the pulse steadily rises and rigidity spreads or if the pain suddenly disappears an immediate surgical operation is indicated. If the case is brought later than forty eight hours after onset the probable consequences are that the patient may go downhill, rally or get better. In such cases complications such as generalised peritonitis due to perforation and gangrene may supervene. The risk of operation must in all cases be undertaken if the condition of the patient gets worse. If a lump is found to be forming in the appendicular region and the condition of the patient is stationary, operation may be postponed. In that case if operation is undertaken, the protective barriers will be broken and the resting condition will flare up. The patient may be operated upon, generally three months after the subsidence of such an attack. The urgency of operation is much lessened if

cases are seen later still, about the fifth, sixth and seventh days after onset. The patient will either be very definitely improving or else probably getting an abscess. In the former case, operation can be withheld until he has recovered and in the latter case though the abscess will need an evacuation there is often no very great urgency about it for a few hours or days, and it will in fact sometimes be wiser to wait for a short period to allow the abscess to come nearer to the surface. Acute salpingitis and acute pancreatitis present considerable difficulty for a correct diagnosis. Immediate operation is not generally suggested and one can wait till an abscess forms. Many acute cholecystitis cases will gradually settle down without operation, though this procedure often entails a considerable risk. The condition of the gall bladder serves as a useful guide regarding an urgent operation. A hard, tensely distended gall bladder with the risk of perforation or gangrene often requires an operation and particularly where symptoms increase and demand relief.

In the various forms of organic obstruction, surgery alone will effect a cure. Strangulation, volvulus and intussusception are usually more urgent than obstruction due to growths and pressure of tumours. When the enema result is nil, and a diagnosis of obstruction confirmed, the sooner the operation is undertaken the better. In cases of hæmorrhage due to erosion of a vessel by a spreading ulcer as met with in cases of gastric and duodenal ulcers, the treatment includes absolute rest in bed, stoppage of feeds by mouth, injection of $\frac{1}{4}$ gr. of morphine, administration of glucose and saline by the rectum, an electric bath and sometimes in severe cases of hæmatemesis, a blood-transfusion. Generally medical treatment is of no avail in these abdominal emergencies while on the other hand the safety of the patient is endangered by delay. For details of surgical technique involved in individual cases, reference must be made to works on operative surgery.

AGRANULOCYTOSIS. Agranulocytosis or neutropænia is a recently recognised disease (Schultz 1922) characterised by a septic inflammation of the throat with toxæmia and marked leucopœnia affecting especially the polymorphonuclear cells.

Neutropænia occurs under the following conditions:—

1. Infective diseases such as kala-azar, typhoid, typhus, measles, influenza, mumps, malaria, dengue.
2. Diseases due to physical and chemical agents such as radium particularly the alpha rays, X-rays, arsenic, benzene, arsenobenzol preparations, drugs containing amidopyrine such as veramon, novalgin, gordon, cibalgin, dismenol, compral, allonal, amytal, amidopfen, cichopyrine.
3. Blood diseases such as leucopenic, lymphatic and myeloid leukaemia—the so-called aleukæmic leukaemias.

4. Severe sepsis.

5. Idiopathic neutropenia.

Two types of agranulocytosis are generally recognised, one is a primary type, the aetiology of which is obscure and another, a secondary type which is a direct result of some recognised septic condition. The condition simulates aplastic anaemia aleukæmia, leukæmia, Vincent's anagina, influenza, atypical Hodgkin's disease or diphtheria. Agranulocytosis may also occur as an event in a long illness. Recent work has established that a large number of cases of agranulocytic angina are due to the toxic action of certain drugs such as arsphenamines; dinitrophenols and pyramidon.

The disease is seen more in middle-aged females. It generally starts with general malaise, lassitude, headache and soreness of the throat and the mouth. The condition rapidly progresses to an ulcerative or necrotic stomatitis involving the lips, gums, tongue, tonsils, fauces, pharynx and tongue. Sometimes the skin and the intestines are likewise affected and there is pyrexia and general prostration. The enlarged cervical glands are secondary manifestations to the oral condition. The blood picture is characteristic. The total white-cell count is reduced to very low figures even as low as 100 to 200 per c.mm. and there is an absolute and relative reduction in the number of granulocytes—the neutrophilic, eosinophilic and basophilic polymorphonuclear cells. The red cells; hæmoglobin and platelets are little affected. A few cases show moderate or severe anaemia of the microcytic type and very rarely of the macrocytic type. A chronic type or agranulocytosis has recently been shown to occur without the oral symptoms, the granular cells remaining for a long time between 10 to 30 per cent. with total counts of 4,000 to 6,000 per c.mm. The condition is considered to be due to the non-formation of the granular leucocytes rather than their excessive destruction. The primary cause is thought to be depression of the bone-marrow functions. The evidence of regeneration of the myelopoietic tissues as shown by the myelocytic response favours the view that agranulocytosis is primarily a marrow dyscrasia. The organisms cultured from the throat lesion and blood are not specific causal agents, but are regarded as terminal invaders.

TREATMENT. A thorough inquiry should be made regarding the use of toxic drugs responsible for the production of agranulocytosis, such as benzene, arsenical and gold preparations, dinitro-phenols and the benzamine group of drugs. The use of these drugs should be strictly forbidden. No treatment is of any value in fulminating cases. The different forms of treatment which appear to have beneficial effects are: (1) Repeated transfusions of 250 to 500 c.cm. of citrated blood every other day or at longer intervals. (2) Irradiation of the skeleton with small doses of X-rays. This treatment is based on the law that small doses stimulate, while large doses destroy, radio-sensitive cells.

(3) Injection of leucocytic extract in an attempt to stimulate the reticulo-endothelial system. Hopeful results have recently been obtained from the administration of a mixture of the sodium salts of pentose nucleotides (prepared from nucleic acid). In severe cases 20 c. cm. of pentnucleotide are intramuscularly injected, twice daily, for 3 to 4 days. When the white cell count begins to rise, the dose is reduced to 10 c. cm. In less severe cases 10 c. cm. of the drug is injected twice daily for a week. The total and differential white cell counts should be done daily to note the progress of the disease during the course of treatment. Clinically, cases have been found to improve after such treatment. No untoward effects are known to follow the intramuscular injections of the drug.

Local treatment of the oral lesions include gargles with hydrogen peroxide, sprays with potassium chlorate and swabbing with a solution of copper sulphate (10 gr. to an ounce).

AINHUM. It is a type of band scleroderma affecting the toes and fingers causing rarefying osteitis of the phalanges often of the little toe, more rarely of the fourth and still more rarely of the little finger. It may end in natural amputation of the affected toe. The band which is at first moderately broad becomes deeper and deeper and by pressure gradually absorbs the underlying phalanx, so that the end of the little toe is about twice its normal size. There are no subjective symptoms unless there is ulceration. The course of the disease is obscure. A trophic origin has been suggested while some consider it to be due to hypothyroidism. The lesion may be associated with other lesions of hypertrophic nature, *viz.*, *cutis plicata*, *tylosis*, *pityriasis rubra pilaris*.

TREATMENT. In the early stages, large doses of *thyroid*, *viz.*, 2 gr. thrice daily combined with *parathyroid* 1/20 gr. and *calcium lactate* 10 gr. twice daily are given. During treatment the patient should be kept strictly in bed and the pulse noted every 4 hours; it should not exceed 85 to 95 per minute. This pulse rate should be kept for 3 weeks to get the full effect of hyperthyroidism. If there is any ulceration or secondary infection, it should be treated surgically.

ALLERGY. The word allergy is derived from two Greek words meaning other energy. Von Pirquet coined the term allergy to indicate an altered reaction in man to foreign proteins and implied that an antigen-antibody reaction was its basis in general. Later, the meaning of the term was extended to indicate all forms of hyper-sensitiveness to foreign proteins whether any antigen-antibody reaction was present or not. Allergy has now come to mean 'exaggerated susceptibility to various foreign substances or physical agents that are harmless to the great majority of ordinary normal individuals.' The reaction appears after inhalation, ingestion, injection or skin contact of minute quantities of the substances in question and differs from any toxic action the substance might produce in large doses. This hypersensitiveness may be

spontaneous or may be induced as in serum sickness. Allergy differs from anaphylaxis, which is the term applied to manifestations of hyper sensitiveness in laboratory animals, in that anaphylaxis is always induced and is always due to antigen—antibody reaction. This hypersensitiveness may be manifested at different sites in the body and these different manifestations are given different names. Thus in the respiratory tract we have paroxysmal rhinitis, hay fever, and asthma; in the skin urticaria, giant urticaria, dermatographia and dermatitis venenata, etc.; in the gastro-intestinal tract certain forms of gastritis and vomiting, enteritis, diarrhoea and mucous colitis; in the nervous system migraine and certain cases of epilepsy. Bray considers that certain forms of enuresis are allergic in origin.

The offending substance or substances may be introduced into the body from outside or may be produced in the body itself. Thus it may be inhaled as in hay fever and pollen asthma, may be ingested as in food and drug allergy, may be injected as in serum sickness, or may be brought in contact with the skin as in dermatitis venenata and urticaria or it may be due to physical agents such as heat and cold. A small group of allergic manifestations may be ascribed directly to insect bites and stings. When produced in the body, the offending substances may originate in an infective process within the body or it may owe its origin to some pathological condition of the gut. It appears that infective foci whether of teeth, tonsils, sinuses, bronchi, etc., liberate a substance which circulates and sensitises various tissues and is capable of producing symptoms in either skin, respiratory or gastro-intestinal tracts. In the cases dependent on some pathological conditions of the gut the substance or substances in question either result from the bacterial action on the protein, or the proteins are broken down in some abnormal fashion and the altered protein gains access to the circulation. In the tropics the allergy secondary to some pathological condition of the gut is much more important than any other form of allergy. This is probably due to a lowering of the defence mechanism of the liver caused by intestinal amœbiasis or some other condition causing hepatitis. That the detoxicating and proteopexic functions of the liver are defective in cases of allergy has been shown by Barber and Oriel who have found important biochemical changes in the blood and the urine of allergics.

DIAGNOSIS. 1. *History.* In cases of suspected allergy it is essential to go carefully into the history of the patient. Careful enquiries may elicit many points of great diagnostic value in allergic conditions. (a) Most allergic conditions commence early in life. It is important to find out the age at which the patient first noticed the onset of the condition. (b) A history of inheritance is commonly found in allergic cases. (c) Season of onset and the seasonal variations in the disease are of importance. This may give a clue to the offending flowers and foods, etc. (d) There is a regular periodicity in the early stage

of allergic conditions. If they are severe and persist for several years they tend to become continuous. (e) Association of the disease with some particular place, food, or animal may be elicited. Particular attention should be paid to the surroundings at home and work, such as presence of factories and stables near at hand, presence of or association with pets and poultry, horses or cows, presence of pillow cases stuffed with chicken feathers, etc. As regards food, at times the provocative articles of diet can be named by the patient, but in the majority of cases he has to be carefully dieted before any food can be incriminated.

2. *A total and differential blood count* is made, most of the allergic patients have a high blood eosinophilia.

3. *Protein skin tests* are often of value in confirming the diagnosis when a careful history makes it possible to discover a specific substance responsible for the patients' symptoms. When no clue is afforded by the history at all we turn to the routine protein skin tests for help. These tests are based on the fact that those substances, which when inhaled, ingested or taken into the body by any other means are capable of producing allergic symptoms, will also produce an urticarial wheal when brought in contact with the lower layers of skin.

The dermal tests are usually done on the forearm. The forearm is carefully cleansed with alcohol and scratches are made on it transverse to the long axis of the arm. The scratches are made only $1/8$ th of an inch in length and they are made without drawing blood. One spare scratch is made to serve as a control. A drop of N/10 sodium hydroxide solution is put on each scratch and the substance to be tested is rubbed into them, one substance into one scratch, the control scratch receives no substance. After fifteen to twenty minutes the test fluid is wiped away and results are read by comparing the site of each scratch with the control. A positive result is denoted by the appearance of an urticarial wheal at the site of the scratch. The material for testing can be purchased ready made or can be made in the laboratory.

The supernatant fluid obtained by macerating a small amount of the substance in a small quantity of N/10 sodium hydroxide solution can be used for the test. A better way for preparing an extract for dermal tests is to extract it with Coca's fluid. Coca's fluid is made by dissolving sodium chloride 10 gm., sodium bicarbonate 15.8 gm. and carbolic acid 8 gm. in two litres of distilled water. Before extracting house dust it should be washed in ether to remove fatty matter and then a 1 per cent. extract in this fluid is made. The extract should then be filtered through a porcelain filter and the filtrate should be tested for sterility (aerobically and anaerobically) before it is used for the test. The test should be performed with very weak dilutions to avoid undesirable effects. It is best to commence testing with one in a million dilution.

4. *Praxisnitz Kustner reaction*. When it is not advisable or practicable to do the usual skin tests as in infants, nervous patients, patients with interfering skin lesions or extremely dermatographic skin or where

the patients cannot attend for testing on account of distance or illness, Prausnitz Kustner reaction which is a reaction by proxy is tested. This consists in injecting a small quantity of the serum from an allergic patient intradermally into a non-sensitive subject and then testing the site of injection with antigens which the allergic patient is thought to be sensitive to.

Five to ten c. cm. of the blood is withdrawn from the patient and the serum is separated with aseptic precautions. The forearm of the subject on whom the test is to be done is cleansed with alcohol and the serum of the donor is injected at two or more sites depending on the number of proteins to be tested. About 1/10th of a c.cm. of the serum is used for each injection and the site of injection is marked with ink or marking pencil. At least two or three hours should be allowed for the serum to be completely absorbed. Then each site may be tested locally for specific proteins.

5. The best proof of a substance being responsible for the allergic symptoms of a patient is that the substance when brought in contact with the patient should precipitate an attack.

6. In most of the cases of allergy a hypodermic injection of 1/1000 solution of adrenalin hydrochloride relieves the symptoms and this forms a good therapeutic test.

7. *The ether reaction for proteoses in urine.* Oriel has described a reaction that occurs with great frequency during allergic conditions. If the urine from cases of allergic and febrile diseases is acidified with sulphuric acid and shaken with a fifth of its volume of ether, the ethereal layer formed on standing, instead of being clear as in normal people becomes opaque and has a waxy appearance. In strongly positive cases the tube may be inverted without spilling the contents.

If the reaction is carried on in a separating funnel and the lower layer consisting of urine is run off, the supernatant layer when shaken with an equal volume of alcohol yields a precipitate of a nitrogenous substance which has been called 'proteose.' The proteose is supposed to be the secondary antigen produced by the action of the sensitised liver cells on the primary antigen and has been used for desensitising the patient. In this connection the work of Manwaring is interesting. He proved that the liver of a sensitive dog produced a secondary antigen which was an alteration product of the original antigen and that this secondary antigen was capable of giving rise to sensitisation. A twenty-four hours specimen of urine is collected from a case showing active symptoms and a little of chloroform is added as a preservative. Approximately 400 c.cm. is placed in a separating funnel, rendered acid to congo red with sulphuric acid and shaken with 100 c. cm. of ether. Should the specimen contain urates it is rendered alkaline with dilute caustic soda to dissolve them and subsequently made acid. When the two layers are separated, the ethereal layer is treated with an equal volume of alcohol and the precipitate is allowed to settle. The precipitate is then collected by

centrifugalising in sterile centrifuge tubes. It is then suspended in sterile distilled water and again centrifuged, when dry, the precipitate is dissolved in sterile N/10 sodium hydrate solution. The quantity of sodium hydrate required, varies with the case but 2 to 3 c.cm. are usually sufficient. Taking the usual aseptic precautions 1 c. cm. of this solution is added to 9 c. cm. of carbo-saline. The dilution is called 1 in 100. Further dilutions of 1/1,000, 1/10,000, 1/1000,000 and 1/1,000,000 are then made. The sterility of the solutions is then tested by inoculating on agar slopes and incubating for 48 hours. The dilutions are then used for diagnostic and therapeutic purposes.

8. *Examination of stools.* The allergic cases secondary to gut infection may show *Entamoeba histolytica* infection or the presence of the ova of various helminths. The McConky-neutral-red-lactose agar plate may show various non-lactose fermenting bacilli causing post-dysenteric lesions. These findings are rather important from the treatment point of view.

9. *A bacteriological and cultural examination of sputum* is made in cases of respiratory allergy, keeping the Gram-negative bacilli of Ryre specially in view.

10. A thorough search is made for any *focus of sepsis* which may be present in teeth, tonsils, nasal sinuses, gall bladder, appendix or genito-urinary tracts.

11. *A fractional test meal* usually shows hypochlorhydria specially in children. This finding may be an important factor in the production of allergy.

Walzer and Walker while working on urticaria found that the Prausnitz-Kustner reaction was more likely to be positive when hypo- or achlorhydria was present and that it often failed in the presence of hyperchlorhydria. This observation is of importance as the work of Schloss in marasmic children has shown that protein in a form capable of producing active sensitisation may be absorbed from the intestinal tract. It is quite reasonable to assume that the absorption is more likely to take place when the digestion is delayed and the proteins are incompletely broken down than when the digestion is complete.

12. Important biochemical changes in the blood and urine are found during the attack. Hurst has suggested that in asthma there is some alteration in blood chemistry which renders an asthmatic subject liable to an attack of asthma from stimuli which in a normal person would produce no response.

Barber and Oriel have found that the amino-acid content of the blood is raised during acute paroxysms of allergic manifestations and blood chlorides seem to be markedly diminished. Similar changes have been found in urine; immediately before and during the paroxysms there is a decrease in urinary output accompanied by an increase in free acid and ammonia and diminution in chloride excretion. Following the

paroxysm the quantity of urine is increased and the urine becomes less acid or even alkaline and contains excess of chloride.

Liver function tests. Experiments of Manwaring demonstrated that the liver was the site of the anaphylactic reaction in dogs and that shock did not occur when the liver was thrown out of the circulation. It is very probable that liver dysfunction plays an important part in the production of allergy specially in cases of intestinal origin in man. Osman suggested that in asthmatic children there is a diminution of glycogen reserve. The proteopexic function of the liver, *i.e.*, its power of fixing protein and its derivatives appears to depend on an adequate supply of glycogen. In the absence of an adequate amount of glycogen in the liver, proteins tend to pass the barrier of the liver and gain access to the general circulation. If this inadequate proteopexic function of the liver is combined with hypochlorhydria which makes the absorption of protein capable of producing sensitisation more likely, the chances of such proteins reaching the circulation are much increased. Bray found in a series of 55 allergics that manifestations of liver dysfunction were twice as common in patients with some gastric dysfunction as in normals. Apart from this proteopexic function the detoxicating function of the liver is also to be taken into consideration. It transforms products of protein digestion into urea and renders non-toxic the products of bacterial action on undigested proteins. The biochemical findings in the blood and urine of allergics provide ample evidence of a basic toxic factor in these conditions. The chief source of this toxicosis is the bowel and the inadequate detoxicating function of the liver allows the toxins to pass into the general circulation.

It can be safely assumed that the allergic reactions of man specially those of intestinal origin depend to a large extent on liver dysfunction, but it is rather difficult to measure the extent of liver damage by means of the laboratory tests for hepatic functions. This is due to the multiplicity of functions with which the liver is endowed and to the wide margin of safety that it has got. An idea of the efficiency of the liver may be obtained by a correlation of several tests.

TREATMENT. Immediate treatment. An intramuscular injection of adrenalin hydrochloride is most effective in relieving the acute allergic symptoms. The earlier the injection is given the smaller is the dose required. Adequate local treatment is given for the skin, nasal and ocular conditions. For the skin calamine liniment and Lassar's paste usually suit but some people may be sensitive to these drugs. For the itching and burning of the eyes Feinberg recommended the following eye-drops: adrenalin (1:10,00) 1.0 c. cm., dilute acetic acid 0.3 c. cm. resorcin 0.3 gm., distilled water 32.2 c. cm. For the local treatment of the nose Bray recommends the following ointment: menthol 2 gm., eucalyptol 5 min., adrenalin chloride 1/20 gr., ephedrine sulphate 5 gm., and soft white paraffin upto 1 oz. A little ointment is to be smeared in the nose several times a day. A mixture containing potassium iodide

and antispasmodics such as lobelia, belladonna, kuth, tinct. ephedra vulgaris, etc., is given between the attacks in cases of asthma.

Treatment of the allergic state. The proper treatment of the condition depends on the results of the investigation of the patient. If the history, skin reactions or elimination diets give a clue to specific sensitisation the following lines may be adopted:—

(a) Avoidance or removal of the cause. To avoid or remove the specific cause is the ideal method of treatment but is practicable only in a minority of cases. Specific foods may be completely avoided. In cases of animal emanations the pets should be removed, hairs and feathers in bedding and pillows may be substituted by cotton, etc. Dust and pollen are most difficult to avoid unless an allergen-free cubicle or an allergen-free mask is used. A change to a hill station of 4,000 to 7,000 ft. altitude is very beneficial in this connection as the atmosphere at this height is free from air-borne allergens.

(b) Specific desensitisation. Next to avoidance comes specific desensitisation. Results with desensitisation are never so satisfactory as with avoiding the cause. It is to be used in those cases in which the specific causes cannot be avoided or removed entirely as when many common articles of diet are involved or when the sensitiveness of the patient is dependent on some occupation which he is not in a position to leave. Specific desensitisation may be attempted by ingestion of gradually increasing doses when the allergen is a common food. The treatment is commenced with a very small amount of food. It is given daily and then the doses are increased very slowly. In cases of allergy due to dust or pollen or animal emanations desensitisation is carried on by repeated subcutaneous injections of the sterile extract made from the substance. The protease isolated from the urine of the patient may be used for specific desensitisation. It is always necessary to ascertain the reaction of the patient to different dilutions before any therapeutic injections are given. The dermal tests are made on patients with different dilutions and the dose for intradermal injection is regulated accordingly. Injections are given first bi-weekly and later once a week, the dose is increased very cautiously.

Along with avoiding the cause or desensitisation the co-existing infections or abnormalities of the respiratory or the gastro-intestinal tract should be adequately treated. Desensitisation with ingestion of small doses of a food gives better results if the food is given with a small amount of hydrochloric acid and pepsin.

Other measures. In the majority of cases even a thorough investigation would fail to incriminate any particular food, animal emanations, etc. In such cases the treatment is to be carried out on the following lines.

In allergy of alimentary origin the antigen absorbed may not be a whole food protein, but there may be toxins liberated by the action of bacteria on incompletely digested proteins which may be the cause of

the conditions or the proteins may be broken down in an abnormal fashion and the altered proteins pass up to the liver whose proteopexic function is deficient and thus they gain access to the general circulation. In treating such cases at least four factors have to be taken into account.

(1) Any infection found in the gut has to be carefully treated. The *Entamoeba histolytica* infection is treated with emetine or carbarson, the hookworm infection is got rid off with carbon tetrachloride; an autovaccine is needed to confer immunity against the pathogenic organisms isolated from the stools. Intestinal stasis if present should be adequately dealt with. (2) An acid-pepsin mixture is of great benefit when there is evidence of hypochlorhydria. (3) The patient should be kept on more or less vegetarian diet, meat and fish should be cut down to a minimum. (4) The liver should be well looked after. Adam advocates acid liver mixture after meals and a weekly blue pill along with balancing the diet. In order to improve the proteopexic function of the liver which depends on its glycogen reserve, Oriel recommends 2 to 4 oz. of glucose to be taken daily in divided doses. Glucose may be taken with meals or dissolved in water and flavoured with orange or lemon juice or it can be taken morning and evening on an empty stomach.

A thorough search should be made for any focus of infection in the teeth, tonsils, sinuses, bronchi, gall bladder, etc. Such foci as can be removed should be dealt with surgically. When the source of infection cannot be completely eradicated, autovaccine prepared from the organism isolated from the focus should be used. Special significance is attached to the vaccine prepared from the Gram-negative bacilli isolated from the sputum. Knott and Oriel have found that these bacilli during their growth in the bronchi produce histamine. Oriel considers that local production of histamine in the bronchi in addition to causing a contraction of the plain muscle surrounding the bronchi would also tend to increase the permeability of the epithelium lining the bronchioles and facilitate the entrance of foreign proteins and possibly bacteria.

Non-specific desensitisation or protein shock therapy. Many substances have been used for this purpose with varying results in the hands of different workers.

Peptone. Auld recommends intramuscular or intravenous injection of peptone. He uses Armour's No. 2 peptone and makes a 5 per cent. solution for intravenous injection and a 7½ per cent. solution for intramuscular use. Both the intramuscular and the intravenous injections are given every fourth or fifth day in the following doses :—

1st dose	...	0.3 c. cm.	6th dose	...	1.3 c. cm.
2nd "	...	0.5 c. cm.	7th "	}	...
3rd "	...	0.7 c. cm.	8th "		
4th "	...	0.8 c. cm.	9th "		
5th "	...	0.9 c. cm.	10th "		

After the tenth dose a few further injections are given weekly reducing the strength of each dose. In resistant cases Auld uses serum peptone agar. After about 4 hours of fasting 4 or 5 oz. of blood are removed in a sterile tube from the arm of the patient. This blood is left at room temperature till the next day, when the serum is pipetted off into another tube. To each ounce of the serum is added 24 gr. of Armour's No. 2 peptone, 6 min. of a well boiled solution of agar containing 1 gr. of agar in 60 c.cm. of water and 4 min. of chloroform. Then the tube is put in an incubator at 37°C. for two to three hours. It is then left at room temperature till the next day when the supernatant fluid is pipetted off. Treatment with this serum peptone agar is begun with a dose of 10 min. intravenously, going up by 5 min. each time until a dose of about 50 min. is reached. Injections are given once or twice a week.

Auto-hæmotherapy. Blood is withdrawn from a vein at the elbow and is reinjected subcutaneously or intramuscularly, whole blood, defibrinated blood, or freshly separated serum may be used for this purpose. The initial dose is 2 c.cm. and the injections are repeated in increasing doses at intervals of two to seven days until a dose of 10 c.cm. is reached.

Milk. Schiff suggested injections of milk. Two ounces of milk are sterilised in a rubber-capped bottle by boiling for 1 hour. Injections are given intramuscularly three times a week commencing with a dose of 0.5 c.cm. and increasing by 0.5 c.cm. until a dose of 8 c.cm. is reached.

Tuberculin. Treatment by tuberculin is specially recommended by Van Leeuwen. The success does not depend on the specific action of tuberculin but on the local reaction produced by the injection of tuberculin. A von Pirquet test is first made to ascertain the degree of sensitivity of the patient and the doses are regulated accordingly. In very sensitive cases the commencing dose should be one-hundredth million of a milligram and it should be increased very cautiously. In other cases the commencing dose can be from 1/10,000,000 to 1/1,000,000 of a mgm.

T. A. B. vaccine. The T. A. B. vaccine has been recommended to be given intravenously every five days. The commencing dose is 50 million organisms, followed by 100 million and increasing by 100 million until a dose of 500 million is reached.

Sulphur. Van Leeuwen uses a 1 per cent. suspension of sulphur in olive oil injecting 1 c. cm. intramuscularly. This is usually followed by a painful local reaction, fever, malaise, etc. The dose in such cases may be reduced and then repeated.

Endocrine therapy. In cases of allergy in which an endocrine basis is suggested gland therapy may be of value. The suprarenals, thyroid, and sex glands are most commonly involved. The desiccated glands may

be given by mouth. Injections of arsenical preparations such as soamine are used to tone up the endocrine system.

AMOEBIASIS. **DIAGNOSIS.** *Stools.* The stool must be fresh and free from urine, oil, and antiseptics. If possible, the whole stool should be sent for examination: (a) Note the macroscopic appearance; (b) test the reaction, and (c) examine under the microscope—(i) fresh preparation in saline, (ii) fresh preparation in iodine, (d) culture, (e) stain by Heidenhan's method when identification is difficult. Repeated daily examinations are often necessary for accurate diagnosis.

TREATMENT. (Acute cases). *Emetine* (see page 368). *Kurchi-bismuth-iodide* (see page 403). *Liquid extract of kurchi* (see page 402). The extract may be given alone or may be combined with 'Isapaghula' (*Plantago ovata*) (see page 416). Care should be taken to keep the bowels acting. *Emetine-bismuth-iodide* (see page 381). *Carbarsone* (see page 411).

In chronic cases complicated with secondary organisms the patients are immunised with a course of autovaccine prepared from the pathogenic bacteria found in the stool either before or during the specific treatment of amoebiasis. Complications like hepatitis, etc., should be treated with emetine injections only.

Intestinal flagellates. In giardiasis stovarsol in doses of 4 gr. (0.25 gm.) twice a day for 10 days before food is recommended. Carbarsone and treparson may be given by the mouth. See page 651.

ANÆMIA. The term anæmia is applied to the condition in which there is reduction of red blood cells and hæmoglobin or of the amount of blood as a whole. *Oligocythæmia* means diminution of the number of red cells. *Oligæmia* means a diminished total amount of blood, while *oligochromæmia* means diminution in the amount of hæmoglobin. Anæmia occurs either as a result of hæmorrhage, the destructive action of a toxin or the decreased vitality of blood-forming organs or deficiency of certain internal secretions.

There are various classifications of anæmia, many of which are imperfect. The following classification by Davidson is satisfactory.

1. *Nutritional deficiency anæmias.* (a) Due to defective production or faulty assimilation of the specific anti-anæmic material found in the liver.

(i) Primary macrocytic hyperchromic anæmia, i.e., pernicious anæmia. (ii) Secondary macrocytic hyperchromic anæmia, i.e., due to sprue, bothrioccephalus, cancer of the stomach, multiple anastomoses, gastrectomy, pernicious anæmia of pregnancy (increased demand, i.e., relative insufficiency), dysentery, etc.

Many cases of the diseases in Group (a, ii) have a failure in iron assimilation and thus pass into Group (b, ii).

(b) Due to defective absorption and assimilation or reduced intake of the factors necessary for hæmoglobin formation. (i) Primary

microcytic hypochromic anæmia, *viz.*, simple achlorhydric anæmia and the Plummer Vin^{cent} syndrome. (ii) Secondary microcytic hypochromic anæmia, due to starvation, insufficient or defective dietary, *e.g.*, diet low in protein and green vegetables, high carbohydrate diet or milk diet. This may also follow inflammation and catarrh of the stomach and intestines (*vide a, ii*).

II. *Post-hæmorrhagic anæmia*. Acute or chronic, including blood loss from the gastro-intestinal, urogenital, and respiratory tracts.

III. *Hæmolytic anæmias*. (a) From acute, sudden, and severe hæmolysis, with hæmoglobinæmia and hæmoglobinuria, *e.g.*, malaria and blackwater fever, paroxysmal hæmoglobinuria, hæmolytic streptococcal septicæmia, hæmolytic poisons, such as toluylendiamine, snake venom, etc.

(b) From steady and incessant hæmolysis associated with excessive activity of the reticulo-endothelial system, leading to icterus and splenomegaly.

(i) Congenital acholuric jaundice and sickle-celled anæmia. (ii) Acquired hæmolytic jaundice:

1. Causal factor unknown. The condition resembles clinically the congenital type, but fragility is less marked or absent.

2. Associated with profound dyscrasias of the hæmatopoietic and reticulo-endothelial systems, *e.g.*, certain cases of Hodgkin's disease and obscure affections of the liver and spleen.

IV. *Anæmias due to depression of bone-marrow function*. (a) Idiopathic aplastic anæmia and idiopathic agranulocytic anæmia. (b) Aplastic or partially aplastic anæmias secondary to radio-active substances, benzol poisoning, toxæmias and septicæmias, cachectic states, cirrhosis of liver and spleen, metabolic diseases (nephritis), and metallic poisons such as lead and mercury.

It is admitted that no classification is perfect, since several factors may be present in any individual case of anæmia. Thus a case of cancer of the stomach may lose blood by hæmorrhage, may be on a defective milk diet, and may have a depressed condition of the bone marrow secondary to cachexia. Nevertheless, the above classification gives a scheme suitable for diagnosis and treatment.

Thus the anæmias in Group I (a) are all macrocytic hyperchromic diseases requiring the administration of liver, liver extract or ventriculin.

The anæmias in Group I (b) and in Group II are microcytic hypochromic anæmias, and require a well balanced diet with massive doses of iron.

In group III the essential treatment is the removal, where possible of the factor causing hæmolysis, *e.g.*, splenectomy in acholuric jaundice and quinine therapy in malaria.

In group IV the guide to proper treatment is an understanding of the underlying causal factor, *e.g.*, change in occupation of workers with benzol and radioactive substances, splenectomy in splenic

anæmia, etc. In addition, stimulation of the depressed bone marrow by blood transfusion and liver and iron therapy should be carried out.

Hyperchromic anæmia is profoundly related to disturbance of gastric secretion. In primary hyperchromic anæmia there is as a rule a complete disappearance of normal gastric secretion, in other words, a true achylia gastrica is present. No free hydrochloric acid has been found even after an intramuscular injection of 1 c.cm. of 0.1 per cent. solution of histamine.

In the hypochromic anæmias achlorhydria is not absolutely invariable. The amount of pepsin is diminished, but the renine-like ferment, which is absent in the hyperchromic anæmias, can be demonstrated to be still present.

It appears then that many chronic types of anæmias described, may be translated in terms of dysfunction of the stomach and intestines. This explains the curious over-lapping in the blood changes which sometimes occurs. A hypochromic anæmia may eventually become hyperchromic as the secretory function of the stomach gradually fails, whilst the efficient treatment of a hyperchromic anæmia may reveal a hypochromic anæmia.

It was formerly held that life in the tropics favoured the production of anæmia but this idea is no longer tenable. Tropical anæmia is a vague term about which there is very little definite knowledge. This diagnosis should never be made until other causes of anæmia have been excluded; the most important of these are malaria, hook-worm disease, dysentery, kala-azar, etc. Mental and physical weakness, pallor, palpitation, œdema of the feet and emaciation are characteristics of this disease.

Pernicious anæmia. DIAGNOSIS. I. *Blood*—(a) Red blood corpuscles are diminished in number; hæmoglobin per corpuscle is increased. The colour index is therefore high (greater than one). (b) The red cells show anisocytosis, poikilocytosis, polychromatophilia and punctuate basophilia; normoblasts and megaloblasts are present. (c) The platelets are reduced. (d) Reticulocytes are increased to 2 per cent. (e) Slight leucopenia with relative lymphocytosis. (f) The polymorphonuclear leucocytes show a 'shift to the right' in the Arneth count, many having 4 or 5 lobed nuclei. (g) Van den Bergh's reaction (indirect) is often positive. (h) Inequality in the size of the red cells in pernicious anæmia is a characteristic feature of the disease. Price-Jones elaborated a method for graphical demonstration of the size of the red cells. In pernicious anæmia the mean diameter of red cells is 8.24μ . (i) Halometric determination of the size of the red cells can also be conveniently employed. (See technique under blood). Price-Jones claims that the degree of anisocytosis is more important than the mean diameter, and that halometer affords no information as to the amount of anisocytosis.

II. *Urine and fæces* contain excess of urobilin.

III. *Test meal* shows achylia gastrica, no free HCl being secreted after histamine injection. The juice also lacks in pepsin and the 'intrinsic factor' of Castle.

IV. *Clinically*, lemon-tint colour of the skin and absence of wasting are important.

TREATMENT. Recent experimental and chemical studies of anæmias have brought to light many factors which control red cell formation in the bone marrow. A special hæmatinic principle is necessary for the development of the megaloblast to the erythroblast stage. Iron, copper, thyroxin and vitamin C are also needed for satisfactory maturation of red cells.

The state of arrested development in the red marrow is due to the absence of what may be called a mating principle. It is normally formed in the stomach by the interaction of an agent present in gastric juice ('intrinsic factor') with another substance found in the ox muscle and which may be identical with vitamin B₁₂ (extrinsic factor). This principle is mainly stored up in the liver. Absence of the hæmatinic principle may lead to a failure in the megaloblastic maturation resulting in anæmia. The principle of treatment of anæmia must therefore be directed towards the supply of the hæmatinic mating principle. In the following lines the different therapeutic agents are discussed.

Liver therapy. The discovery of liver as a therapeutic agent in pernicious anæmia by Minot and Murphy in 1926 is perhaps the greatest advance in medical treatment of anæmia. The specific substance required to enable the bone marrow to function normally as regards the formation and maturation of red cells may be supplied by taking liver by mouth, either raw or cooked. Any mammalian liver is effective. Cooking does not destroy the active substance provided the liver is not subjected to prolonged boiling. The quantity of liver required varies in individual cases, but as a rule $\frac{1}{2}$ lb. daily is needed at the beginning of treatment. The liver extracts, of which there are many preparations on the market, are equally effective but more expensive, and are rarely necessary except perhaps at the beginning of treatment when the patient cannot tolerate the large amount necessary to induce a remission.

Striking blood changes occur with the institution of liver feeding which are especially marked when the patient is very anæmic. Reticulated red cells which in the blood of the untreated patient usually do not exceed 2 to 3 per cent. of the red cells, begin to increase in number within a few days of the beginning of treatment, and by about the 10th day have usually risen to anything between 15 to 40 per cent. Subsequently the percentage of these reticulated cells, or reticulocytes as they are often called, begins to fall and within a few

weeks returns to the normal. With the rise in the percentage of reticulocytes the number of red cells begins to increase and this continues until in the course of four to six months it approximates to normal. There is a coincident rise in the hæmoglobin and the colour index approximates to normal. With the changes in the blood there is a steady improvement in the condition of the patient.

The continuous consumption of large quantities of liver is inconvenient and generally distasteful. It has been shown that the activity is retained by deproteinated aqueous extracts which may be greatly concentrated and which are not disagreeable to take. Liver extract No. 343 is a powdered concentrate of this sort; several other liquid and dry extracts are on the market.

Liver extract No. 343 is a water-soluble nitrogenous, non-protein fraction obtained from fresh mammalian liver. It is supplied in vials containing an amount of powder (3 to 4 gm.) representing 100 gm. of fresh liver. It is administered orally in water, soup, orange juice or other vehicle about an ounce per vial. The initial dose is five to eight vials. When the blood has been brought to normal, the dosage may be reduced to the maintenance level, usually two or three vials per day, controlled by monthly blood examination.

Liver preparations for intravenous and intramuscular injections can be safely administered to patients with satisfactory results. The intramuscular method is almost as rapid in action as the intravenous method and does not produce any reaction; hence it must be considered to be the method of choice. The majority of workers use preparations of a bulk of 5 c.cm. which contain the extract from 100 gm. of liver. *Hepatrat* and *Camipolon* are some of these preparations used at present.

One of the causes of failure of liver treatment is the presence of a septic focus, and the commonest infection of any importance is pyelitis. Every patient with pernicious anæmia who fails to respond to injections of liver extract should have a bacteriological examination of a catheter specimen of urine done. Once such urinary focus of infection is cured, liver will exert its usual effect. Hypothyroidism is another common cause. If liver extract has failed to bring the blood to normal, small doses of thyroid extract may be given in addition with encouraging results. Presence of arterio-sclerosis is also a cause of failure, though to a partial extent. This is one of the most troublesome complications and in the absence of efficacious treatment of arterio-sclerosis, larger and larger doses of liver extract is required. In pernicious anæmia blood destruction occurs and it is often assumed that the iron derived from this source will be enough to furnish hæmoglobin for a normal number of corpuscles. But this is not true in every case and it may be necessary in some cases to supplement liver with a course of iron to keep the hæmoglobin and red corpuscles a normal figure.

Stomach preparations. The occurrence of achlorhydria in pernicious anæmia suggests a possibility of causal relationship with gastric functions. The work of Castle showed that meat previously digested in a normal human stomach and then fed to a pernicious anæmia patient is effectual in the treatment of this condition. The use of desiccated pig stomach has also given good results. The therapeutic response is identical with that of the liver extract, quite uniform and even somewhat more prompt.

Ventriculin N. N. R. is prepared by grinding the entire stomach of hogs, drying in vacuum below 66°C. and extracting the fat contents therein. It is standardised by clinical tests, so that 10 gm. of the dried stomach correspond in activity to 300 gm. of the fresh liver. It is taken stirred with water, in which it is insoluble. The daily dose is 10 gm. per million deficit in the cell count. The maintenance dose is 10 gm. per day.

Iron. Iron is seldom required in the treatment of pernicious anæmia. In a small group of cases it is a very important adjuvant to liver therapy.

Hydrochloric acid. It is a valuable drug in the treatment of vomiting and dyspepsia and especially of the diarrhoea which is a common complication of the achlorhydric state; 1 dr. of dilute hydrochloric acid, three times a day, well diluted with water and flavoured with orange juice, often works like a charm. Glycerine of pepsin B. P. may be added to it with advantage.

SUMMARY OF TREATMENT. The present position regarding the treatment of pernicious anæmia may be summarised shortly as follows: The complicated diet, as originally suggested by Minot and Murphy, is now unnecessary, but a liberal well-balanced diet rich in protein is essential. The following is shown by Whipple to be of value in blood regeneration. (1) An adequate daily intake of red meats, green vegetables, and fruits. (2) Liver, either raw pulp or lightly cooked. The amount required for a case of average severity is about half a pound daily. (3) Liver extract derived from 500 gm. of whole liver, or desiccated hog's stomach, 10 gm. for every million red cells deficient, is of particular service during the severe relapsed stage. When nausea and vomiting are prominent features, intramuscular or intravenous liver extract therapy is of particular value. Liver extract or desiccated hog's stomach may be used as a substitute for whole liver during the remission stage, but it should be remembered that whole liver appears to have certain definite advantages over such preparations and therefore should still be considered as the staple article in the maintenance diet. (4) The maintenance dose of effective principle must be taken for life. It varies in individual cases widely as already described, but generally speaking, from one and a half to two pounds of liver per week is sufficient. The only criterion on which to judge the maintenance dose is the blood level. The difficulty in some cases of bringing the blood level

to normal and the dangers consequent on the failure to do so have already been discussed. (5) After preliminary treatment with liver, septic foci, if present, should be adequately dealt with. (6) No drugs are required for routine purposes, but in certain particular conditions hydrochloric acid, iron, and thyroid extract may be of service.

Microcytic hypochromic anæmia. As already indicated in the classification, microcytic anæmia may result from widely different causes, although the blood picture present may be essentially similar. All are agreed that it is wrong to treat such anæmias without diligently hunting for and if possible eradicating the cause. Microcytic hypochromic anæmia results from a deficiency of the hæmoglobin building factors, because of inadequate intake, faulty assimilation, or excessive loss, and the anæmia can be relieved by iron medication, by suitable dietary or by a combination of the two. A brief review of the facts on which our present knowledge regarding the importance of nutrition in the production, prevention, and treatment of microcytic anæmia is based, is, therefore, deemed desirable.

For the maintenance of health an adequate diet is required, which may be summarised briefly as follows. (1) The caloric value should be sufficient to keep the body weight within 10 per cent. of the normal. (2) Protein must be of good quality. Minimum requirement is two-thirds of a gramme per kilo. of body weight. Average amount, 12 to 15 per cent. of the total calories of the diet (from 60 to 120 gm. per day). (3) The carbohydrate must be enough to allow for energy and to avoid ketosis. Average amount is 50 to 55 per cent. of the total calories of the diet (from 200 to 500 gm.). Fat is required for heat and energy, and as a carrier of the fat-soluble vitamins. Average amount 30 to 33 per cent. of total calories of the diet (80 to 120 gm.). (5) There must be a good supply of vitamins A, B, C, D, and E. (6) There should be an adequate amount and a proper balance of the necessary mineral salts :—*Calcium*. Adults require 0.67 gm. (represented by 1 pint milk) and children require 1.2 gm. (represented by 1 quart milk). *Phosphorus* 1.33 gm. *Iron* 0.015 gm. (7) Enough roughage to give a daily bowel movement without aperients. (8) Water, from four to six glasses daily. (9) The food should be properly cooked and attractively served.

TREATMENT. *Iron.* Administration of iron is indicated particularly in those varieties of anæmia in which the hæmoglobin index is low, *i.e.*, in chlorosis, and cases of secondary forms of anæmia, such as are commonly met with in tuberculosis, syphilis, malignant disease and many other conditions. Anæmias, the result of hæmorrhage, chronic poisoning with lead, mercury and arsenic, the presence of parasites in the intestine or presence of malarial organisms in the blood, are also benefited by iron, though special attention must be paid, in these conditions, to removal of the original cause.

Hæmoglobin may be deficient either because of the defective hæmatopoiesis or by reason of excessive hæmolysis. The best results with iron are obtained in cases belonging to the former class.

Iron appears to act by stimulating the blood formation in the bone marrow, although in normal animals, slight increase occurs in the number of red cells circulating and of the fat in the bone marrow, without any increase of cell formation in the marrow. Successful iron therapy in anæmia depends on giving a suitable iron preparation in adequate dosage. The treatment ought to be continued as a rule, for six weeks to two months, in order to procure all its useful effects. As to the dose, iron and ammonium citrate 30 gr. thrice daily or Bland's pill 45 gr. daily are required. Ferrous sulphate tablets (Glaxo) which contain 3 gr. of iron with copper and manganese in minute doses is found to be efficacious. A dose upto 9 gr. thrice daily can be given. It is easy to administer and the cost of treatment is also very low.

Iron therapy is totally ineffective in pernicious anæmia; indeed it appears that the untreated patients have more iron available than can be used in the diminished manufacture of red blood corpuscles; for the colour index is high and the reserve iron of the liver and spleen is considerably increased.

Copper. The role played by copper in the cure of hypochromic anæmias is distinctly a minor one. Whilst certain experimental results suggest that it acts as an adjuvant to iron, the evidence is conflicting. In any case, a well-balanced dietary includes sufficient copper. Copper and ammonia sulphate were empirically tried in doses of 0.03 to 0.12 gm. in the treatment of anæmia that resisted iron, long before recent experiments called attention to its possible value in anæmia. It has been prescribed dissolved in peppermint water sweetened with syrup. Copper acetate, though not an ideal salt for the purpose because of its acetic acid odour and astringent action, might be used in doses from 0.006 to 0.030 gm. Traces of copper which are normally present in food or their addition to artificial diets, aid greatly as a supplement to iron in the formation of hæmoglobin in young animals and in nutritional anæmias.

Radium. The bone marrow, spleen and lymph glands are markedly affected by radiation so that blood picture changes. The hypodermic injection of soluble radium salts produced rapid increase of the red cells, persisting for several weeks. The hæmoglobin did not rise as much. The leucocytes were also increased with small doses.

Arsenic. Small doses of arsenic were found by Stockman to produce hyperæmia of red bone marrow in young animals. Arsenic, however, has a general action in producing dilatation of the capillaries and its action on the red bone marrow may be due to this effect. There is no evidence that arsenic causes any increased formation of

red blood corpuscles in normal animals. Arsenic treatment frequently produces temporary relief, and it is now believed that this effect is due to the arsenic causing the destruction of a certain amount of the patient's liver substance and thus releasing some of the active principles.

Fowler's solution is given orally commencing with 3 min. thrice daily and increasing up to 15 min. The drug is discontinued if there is any symptom of intolerance. Alternately, sodium cacodylate 1 gr. daily may be given intramuscularly. Arsenic may be combined with iron for injection purposes. *Hydrochloric acid* may be used if there is achlorhydria as in primary anaemia.

Splenectomy. Another method of treatment to which much prominence has been given is the excision of the spleen. Splenectomy is done in Banti's disease and in cases of splenomegally of unknown or uncertain origin.

Blood transfusion. The transfusion of 200 to 500 c.cm. of blood from a suitable donor may be of great service when an extreme degree of anaemia is present at the commencement of treatment.

ANGINA PECTORIS. Angina pectoris may be defined as a disturbance of the cardiovascular system with severe substernal pain and generally associated with a sense of oppression or constriction which may reach a high grade of intensity and intolerable anguish. It is associated with other symptoms such as a sense of impending death and an acute misery accompanied by varying vasomotor disorders such as cold sweats and deathly pallor. Angina is common in families associated with an inherited tendency to arterial diseases and hyperpiesia. It is commonly seen in persons of middle age and is commonest in males between the ages of 50 to 70. Good living, lack of sufficient exercise and excessive mental strain are predisposing factors of angina. Diabetes is an important aetiological factor because of the high incidence of generalised arteriosclerosis in such patients, and the increased liability to coronary sclerosis. Syphilis, by causing aortitis, stenosis of the mouths of the coronary vessels and aortic regurgitation, predisposes to anginal attacks. In such syphilitic cases, the capacity of the ventricles is large, the orifice of the coronary vessels is narrowed and the diastolic pressure is low; all these lead to ischaemia of the myocardium. There is special tendency to localized coronary spasm, resulting in angina of the spasmodic type. The essential pathological changes responsible for spasmodic angina are changes in the coronary arteries such as a narrowing of the orifice or lumen of the artery. The pain is really of a physiological nature due to improper nutrition of the heart from organic defect or from temporary spasm. Angina is rarely seen in cases of mitral stenosis and where the auricles are fibrillating. The substernal discomfort or pain is induced by effort and is relieved by rest. The three cardinal symptoms of angina are pain, a fear of impending death and disturbance of respiration. Pain also

has certain lines of radiation the commonest of which is the left arm. Physical examination is generally disappointing in the diagnosis of the condition. A sudden death might ensue from coronary thrombosis. In the hyperpietic group, vascular accidents such as cardiac failure or failure of renal functions may cut life short. The prognosis is grave in families predisposed to angina and essential hyperpiesia.

An electrocardiogram may yield helpful information. A low voltage in all leads, the presence of a branch bundle block, or an abnormal Q R S complex, or evidence of a previous coronary thrombosis, would be an unsatisfactory finding suggesting the presence of myocardial damage and to that extent adding precision to the prognosis.

TREATMENT. Absolute rest is imperative on the slightest sense of substernal discomfort. If the pain does not subside with rest, one or more tablets of trinitrine should be chewed slowly. If this fails to yield relief, the inhalation of amyl nitrite is indicated. If such drugs cannot alleviate the intense pain, morphine may be injected in doses large enough to make the patient comfortable. If, however, the pain proves very resistant and recurs with increasing intensity in spite of rest and opiates, a coronary thrombosis should be suspected. In the less severe attacks, flatulence may be a distressing symptom, and this may be relieved by brandy or a strong carminative draught containing menthol 8 gr., aromatic spirit of ammonia, compound tincture of cardamom and tincture of ginger, each 1 oz.; two teaspoonfuls of this mixture to be given in four tablespoonfuls of water. In cases of frequent recurrent attacks, a mixture containing opium and chloral, given twice daily, may diminish this tendency. In the angina associated with aortic regurgitation, nocturnal attacks are common. In these cases a draught of opium and chloral taken before retiring to bed proves effective. General treatment in these cases is based on the recognition that the circulation through the coronaries is defective and that this defect is permanent and irremediable. Reliance, therefore, must be placed on a change in the mode of life rather than on drugs. A careful investigation should be made not only into the physical condition of the patient, but also into his mode of life and environment, in order to discover the extent of the organic damage. Exercise is advisable to keep the heart muscle fit and walking serves this purpose. As the condition advances, the amount of exercise which can be indulged in with comfort gradually diminishes. Under no circumstances should any sudden or severe physical effort be made. A short rest after even the lightest meal should be insisted upon. With diminution of the cardiac reserve, many patients find comfort and benefit in retiring early to bed at night. Diet is important; meals should be small, the food simple and easily digestible, and a minimum of fluid should be taken with the meal. Obesity should be controlled with strict dietary measures as it often leads to fatty degeneration of the myocardium. Constipation and flatulence should be avoided. In all cases, the examination of

blood for a Wassermann reaction should be a routine procedure, search should be made for all foci of sepsis in the body, and hyperpiesia if present, should be controlled. Large doses of ammonium bromide, 20 gr. twice or thrice daily, are undoubtedly helpful in calming down patients with mental worries. Chloral hydrate 10 gr. twice daily, is also a valuable addition. Luminal $\frac{1}{4}$ gr. or theominal 5 gr. may be administered once or twice daily in restless and eager patients. In syphilitic cases, potassium iodide in full doses should be given and, if possible, mercury by inunction. Large doses of potassium iodide, 30-40 gr. thrice daily, are sometimes very beneficial in diminishing the nocturnal attacks of angina in patients with marked aortic regurgitation. Some authorities prefer intramuscular injections of bismuth preparations to mercury when the Wassermann reaction is positive. Diathermy is said to diminish the number and severity of attacks both in cases of hyperpiesia and in normal pressures. It is best administered with one electrode placed over the sternum and the other between the shoulders. A suitable therapeutic dose is from 800 to 1,500 milliamperes for 20 to 30 minutes twice or thrice a week. Convalescence should be well controlled particularly after toxic illnesses such as influenza. General tonic treatment and hæmatinics are of real value in cases of angina associated with anæmia. Shirley Smith states that he has obtained satisfactory results from the use of insulin and glucose in anginal patients, irrespective of the presence or absence of diabetes.

The principle of surgical treatment consists in cutting off the sensory impulses from the heart and aorta to the nervous system by way of cardiac nerves. The surgical treatment in angina was first adopted by Jonnesco in 1916 who removed the whole sympathetic chain on the left side. Coffey and Brown later suggested a less extensive operation by removing the superior cervical ganglion alone. Eppinger and Hofer found that section of the depressor nerve arising from the vagus and superior laryngeal nerves was beneficial in some cases. Swetlow advocated the paravertebral injection of 5 c.cm. of 85 per cent. alcohol into the upper five intercostal nerves close to the intervetebral foramina. The cessation of pain in such cases may last for several years.

ANTHRAX. See page 1166.

ARTHRITIS. Inflammatory affections of joints are of the most diverse character and are brought about by various factors. Willcox classifies such affections of joints according to ætiological factors as:—

1. **ARTHRITIS OF KNOWN CAUSATION.** (a) *Traumatic arthritis.* A simple trauma, with or without damage to the various structures composing a joint, may bring about inflammatory changes in a joint or it may simply be a predisposing factor to such a change as in subjects with tuberculous diathesis.

(b) *Specific infective arthritis*. Here the exciting cause is generally some organism responsible for systemic diseases, and arthritis develops as a complication in the course of the disease.

Gonococcal arthritis. This is a serious complication in gonorrhœa and usually results from gonococcal septicæmia.

Dysenteric arthritis. It is a common complication in bacillary dysentery and is generally seen after the acute intestinal symptoms have subsided. Such post-dysenteric arthritis is held to be due to secondary infections of the colon with streptococci and other intestinal flora. It is very rare in amœbic dysentery though a few cases are on record.

Pneumococcal arthritis. It occurs in general pneumococcal septicæmia in acute stage of the disease even before the involvement of the lungs.

Tuberculous arthritis. It is generally seen in young patients with a primary tuberculous focus elsewhere in the body.

Scarlatinal arthritis. It is a fairly common occurrence in scarlet fever and varies from mild forms of arthralgia to the severe joint pains.

Malta fever arthritis. Arthralgia, during the initial stage of the disease and effusions into joints, during the relapses, are commonly met with.

Dengue fever arthritis. Effusions into joints accompanied by severe pain in the bones are met with in the course of the disease.

Typhoid arthritis. Arthritis may develop during the later weeks of the acute stage of the disease or a multiple suppurative arthritis may form part of a post-typhoid septicæmia and pyæmia.

Syphilitic arthritis. It is met with both in the congenital and acquired forms of the disease. Effusions into joints in the secondary stage and gummatous thickenings of the structures of joints in the tertiary stage are the common pathological changes in the joints. Relative lack of pain is the essential characteristic of a syphilitic joint.

Arthritis in glanders. The joint is infected with *Bacillus mallei* and arthralgia and suppurative arthritis are the forms seen in the disease.

Septicæmic and pyæmic arthritis. Acute arthritis leading to suppurative changes in the joint is a common complication in septicopyæmic condition of the blood infected with staphylococci, streptococci and other pyogenic organisms.

Filarial arthritis. Among other complications, synovitis, suppurative arthritis and fibrotic ankylosis of joints are seen in the course of the disease.

Arthritis in guinea-worm disease. Sometimes a female dracunculus penetrates a joint and causes synovitis or arthritis.

Arthritis in leprosy. In leprosy, joint involvements present a clinical picture identical with Charcot's joint in tabes dorsalis.

Arthralgia and arthritis are also seen as complications in relapsing fever.

(c) *Arthritis in gout.* The joint never completely recovers after recurrent attacks of arthritis resulting in permanent pathological deformities.

(d) *Arthritis following the injection of animal sera.* Arthritis is a common complication in serum sickness and anaphylactic attacks after serum administration.

(e) *Arthritis of neuropathic type.* Various pathological changes of bones and joints are met with due to trophic changes associated with tabes dorsalis and syringomyelia. Complete absence of pain in the diseased joints is the predominant feature in such cases.

(f) *Arthritis due to abnormal blood conditions.* (i) *Hæmophilia*; Hæmorrhage into joints, with or without an exciting cause, and the resulting arthritis are common in the disease. (ii) *Purpura.* Arthralgia in purpura simplex and arthritis with effusion in joints in purpura rheumatica are the common accompaniments in the disease.

(g) *Arthritis associated with deficiency diseases.* Hæmorrhagic effusions into joints in scurvy and pathological changes of the structures of a joint in rickets are commonly met with.

2. ARTHRITIS OF OBSCURE CAUSATION. (a) *Acute rheumatism.* Here arthritis is one of the diagnostic symptoms in the disease.

(b) *Non-specific infective arthritis.* This includes all the chronic types of arthritis with obscure ætiology, though infection is held to be a factor in its causation and known as rheumatoid arthritis, arthritis deformans, osteo-arthritis and chronic villous arthritis.

The ætiological factors of arthritis of known causation are the same as those causing such diseases, but the factors responsible for the non-specific type are generally obscure. Bad hygienic conditions of living, improper diet, exposure to cold, nervous or emotional shock, a trifling trauma, heredity, all play an important role in the ætiology of the disease. Focal infection, as of the teeth, tonsils, sinuses, genito-urinary passages, is held by the modern school to be a most potent factor in the ætiology of chronic infective arthritis. Cecil (1933) holds that apart from infection, arthritic changes result from many causes more frequently induced by general biologic factors such as chemical, anaphylactic or toxic processes than by infection of the joints. Infections usually remote from the rheumatic joints incite the chemical or toxic processes which cause the change in the joints, yet it is also probably true that other than infectious agents, that is trophic or toxic factors, may produce similar clinical disturbances.

TREATMENT. Burbank (1930), in all cases, suggests a good plan for a thorough investigation of the physical and biochemical conditions of the patient before the rational treatment is commenced. Cultures of organisms, isolated from suspected foci of infections in the system, are made. A complete bacteriological examination of urine and stool, with subsequent identification of all unusual organisms, is undertaken in each case. In every case, blood is taken as for Wasserman's test,

gonococcus fixation and titration against polyvalent antigens of *Streptococcus viridans*, *S. hæmolyticus* and the slow hæmolising type, *Staphylococcus aureus*, *B. coli communis*, and also against thirty-five strains of streptococcus isolated from known active foci in arthritic cases. A blood culture is also done in all cases.

The patient's general health should be kept in the best possible state. A search, to find out the infective foci in the body as in the teeth, tonsils, sinuses, genito-urinary passages, etc., is to be made and prompt measures should be adopted for their eradication. Stasis of food and its subsequent putrefaction in the stomach and the gut are to be avoided. The harbouring of harmful pathological saprophytes in the alimentary canal is best combated by the internal administration of specific drugs against such bacteria. Elimination through the skin, bowels and bladder is to be always encouraged by physical therapy and drugs. Trauma in all forms should be carefully avoided. Complete and perfect rest, both general and local, should be enjoined on the patient in the active stage of the disease. Measures to raise the general resistance of the body, by improved personal hygiene living in a healthy environment, proper dieting with necessary vitamins, increasing the rate of metabolism and stimulating the endocrines of the system should always be advocated. A dry and hot climate is always preferable for arthritic subjects.

Local treatment and physical therapy. Physical methods of treatment in rheumatic and other joint affections have been found to be most effective in general practice and sometimes better results have been obtained than with drug treatment. These methods improve the general health of the patients thus increasing their resisting power both by direct action and indirectly by causing auto-inoculation. In most cases pain is relieved, swelling and stiffness reduced and deformity corrected.

The idea of local treatment is to improve the circulation of the affected part. This is effected by physico-therapeutic measures. Radium, heat, ionisation, massage, exercise, diathermy, heliotherapy—all are invaluable. The affected part should have perfect rest in the acute and subacute stage when active inflammation is present. Resting a joint by splints; elastic bandages and other orthopædic appliances in the acute stage to prevent subsequent deformity should always be borne in mind. The beneficial effects of physiotherapy are due to cutaneous vasodilatation, generalised sweating and pyrexia, whereby the unhealthy state of the skin improves and pain and stiffness of muscles are considerably reduced. Douthwaite (1931) recommends a 'foam bath,' where a patient is placed in water with a temperature of 104°F. and to which a special solution of saponin is added. Air is pumped through and foam envelope the patient. The effect of the 'hot paraffin wax bath' is similar. The profuse sweating after such baths is removed by a hot water douche and the patient is subjected to general massage and muscle kneading. The

most simple and valuable form of thermal treatment consists of the old fashioned hot wet pack, made of blankets wrung out of hot water. A pack is given daily for ten days. No form of thermal treatment is complete unless followed by general deep massage. Local application of heat in form of poultices, hot magnesium sulphate compresses, anti-phlogistin, mud packs, moist heat, exposure to a gas fire containing infra-red rays, a small radiant heat lamp, dry heat in form of electric pads, is beneficial to relieve pain of inflamed joints. Diathermy is a good source of heat whilst if there be much effusion, ionisation with other drugs is useful. Only when the acute stage subsides, gentle massage and graduated exercise to preserve the integrity of blood circulation, electro-therapy in form of Faradism, sinusoidal current or interrupted galvanism, necessary for restoring the function of the part, should be adopted. Any form of exercise which will leave the part painful and tired, half an hour after the cessation of the act, should never be encouraged. Deep X-ray therapy relieves pain in osteo-arthritis.

Diet therapy. The problem of selection of a proper diet for arthritic subjects is a difficult one and is receiving attention every day. Regulation of diet depends on the patient's general condition of health, weight, chemical examination of blood and general clinical progress. The basic diet should be of low caloric value, with low carbohydrate, protein and purine values but of adequate vitamin content. Foods that are not properly digested should be eliminated and easily assimilable, nourishing ones, low in irritants and in carbohydrates (which furnish a good medium for streptococcal growth), substituted.

In the acute stage of the disease, the patient should live on glucose and fruit juice and no liberal diet should be allowed till the acute symptoms subside. Much benefit has been obtained with this, as meanwhile there is generally a marked absorption of pathological exudates in or around the joints, nearly ankylosed by existing fibrous contractions. Persons with atrophic and hypertrophic arthritis have definitely improved on low caloric diets with reduced food intake. Reduction of carbohydrates with adequate substitute of proteins and fats is useful.

Dietetic factors are of great importance, the essential being properly balanced vitamin supply. Deficiency in this induces a lowered state of resistance to rheumatic infection. Many patients with chronic arthritis show an atony and dilatation of the colon and the supply of vitamin B improves such a condition.

About 50 to 100 gm. of raw spleen daily with a salt-free diet have been recommended for tuberculous arthritic subjects. Sometimes about 2 gpn. of the pressed juice of raw spleen reaching a maximum of about 30 gm. daily have also been given with benefit.

Non-specific protein therapy. This is of benefit specially in acute poly-arthritis, gonorrheal arthritis and infectious types of chronic arthritis during the period of active inflammation. If the response to such

treatment is prompt and effective, it is continued at an interval of two days, but, if otherwise, the treatment is generally discontinued. The underlying principle of this therapy is to excite a mild inflammatory reaction with leucocytosis and antibody formation. Sometimes marked improvement has been observed in rheumatoid arthritis and arthritis deformans with intramuscular injections of peptone, the dose being 0.2 gm. and repeated weekly. Injections of skimmed milk or its preparations such as Aolan have also been used with some benefit, the dose is 4 to 10 c. cm. injected intramuscularly and generally repeated twice a week. Artificial production of leucocytosis and antibody formation are also facilitated by intramuscular injections of sodium nucleinate, the dose being 0.05 gm., one per cent. sulphur in suspension in olive oil, and the intravenous use of some bacterial emulsions. Yeoman (1926) has used T. A. B. vaccine intravenously and reports rapid improvement in chronic arthritis cases. The initial dose is 50 millions, increased at each subsequent dose by 100 millions and with an interval of 4 days in between the injections. These injections stimulate the defensive mechanism of the body and the ultimate factor in determining a cure may be the response to the antigenic activity of the infecting organism, this response being evoked not directly but indirectly by the protein injected.

Fever-therapy. In chronic types of arthritis this changes the chronic inflammatory processes of the joints into acute ones, with a better healing tendency as a result of the acidosis produced by it which also aids and stimulates the natural defence of the body by stimulating the hæmopoietic system thereby increasing the leucocytic elements. Horn (1933) employed a preparation, consisting of fever-inducing substances from non-pathogenic bacteria and reports much benefit with such therapy in a considerable number of his cases.

Vaccine therapy. This has given encouraging results in the treatment of arthritis. Definite benefit has been obtained in the polyarticular types of cases of quite long duration. Autogenous vaccines prepared from strains of organisms isolated from infective foci of the patient himself are generally preferable. Douthwaite (1931) treated cases of arthritis with stock vaccine freshly prepared from about forty strains of *Streptococcus viridans* isolated from the teeth and tonsils of patients. The initial dose was 5 to 10 millions injected subcutaneously at intervals of 3 to 4 days but sometimes once a week. The reaction was allowed to subside completely before the repetition of a second dose. Generally on an average, about 8 to 12 injections were given and improvements were marked after such treatment.

Hæmotherapy. Copeman (1932) advocates hæmotherapy in the treatment of arthritis. After proper elimination of septic foci in the body, if no improvement in the condition of the patient is marked, blood sedimentation rate is estimated to detect a hidden focus of infection. Two blood transfusions, each of 500 c.cm., are given at an interval

of 8 days and intense physical treatment is undertaken along with it. The patient is next put on an insulin regimen and the weight observed from time to time. Marked improvement was noticed in many cases.

Drug therapy. Sodium salicylate has long enjoyed the reputation of a good anti-rheumatic drug. It is often used in large doses in rheumatic arthritis. Peters (1929) treated cases of rheumatic polyarthritis with marked benefit with large doses of sodium salicylate; 50 c. cm. of a solution containing 30 gm. of sodium salicylate, 60 gm. of sodium bicarbonate, 300 c. cm. of syrup of orange and distilled water added to make it 1000 c. cm. were given ten times daily at two hourly intervals and then at four hourly intervals only when fever and pains had subsided. A quick cure was marked in acute cases and the accompanying endocarditis improved.

Aspirin. The drug has anti-rheumatic properties and is used as a substitute for salicylic acid and its salts. Repeated doses of the drug such as 5 gr. every 6 hours often lessen rheumatic pain and are useful as an analgesic.

Tylcalsin (calcii aceto-salicylas) in doses of 5 to 15 gr. has given excellent results in gonorrhoeal arthritis. It is an analgesic, antipyretic, a prompt rheumatic specific and a useful substitute for aspirin. Campbell, Pritchard and Burnford advocate its intravenous use in acute and subacute rheumatism. The usual dose is 0.5 gm. in 10 to 20 c.cm. of distilled water and the concentration should never exceed 5 per cent.

Hexamine. McCarthy Morris (1931) advocates the use of hexamine in rheumatoid arthritis in combination with sodium salicylas. He recommends a prescription consisting of hexamine, sodium salicylate and ammonium benzoate, 1 dr. of each; potassium citrate, 6 dr. and chloroform water to six ounces. Half an ounce of the mixture is to be taken in soda water every morning before breakfast. The treatment is generally a prolonged one.

Amidopyrin has been used in the acute stage of the disease, in doses of 0.3 gm., every two hours and repeated eight times a day. The treatment is continued till the acute symptoms subside and then the dose is gradually decreased. It is better than massive doses of sodium salicylate. Generally, nausea, constipation and headache may appear as after-complications of amidopyrine treatment, but cardiac complications are never observed.

Sodium iodide. A 10 per cent. freshly prepared solution of sodium iodide has been used intravenously in chronic rheumatic arthritis with some benefit. About 10 to 15 injections are given with an interval of two days in between the injection. The treatment should not be given if too much reaction is produced and it should be accompanied by intense physical therapy. Syrup ferri iodide in $\frac{1}{4}$ to 1 dr. doses is beneficial in some cases.

Hæmatinics. As anæmia is an accompaniment of chronic arthritis, iron and arsenic in form of organic preparations are always indicated

to restore the normal level of the blood. Calcium, viosterol and similar other preparations are also useful, as there is generally a drain of calcium from the body in the disease for the elimination of oxalic acid from the system.

Thiosinamin et sodii salicylas is used as an intramuscular injection in rheumatoid arthritis for relaxing scar tissue. One c.cm. contains approximately 0.06 gm. of thiosinamin and 0.09 gm. of sodii salicylas.

Aurotherapy. It was the similarity between tuberculosis and rheumatoid arthritis which led Forestier (1928) to try the effects of gold salts in the latter disease. He used two synthetic preparations of gold.

1. *Allochrysine* (sodium aurothiopropionol sulphonate) is given as an intramuscular injection. A course begins with 3 injections of 0.05 gm. each at intervals of 5 days and if no reaction occurs, further injections of 0.1 gm. each should be continued weekly until a total amount of 1.5 or 2.0 gm. is given. Such a course takes about 3 months and no more than 2.0 gm. should be given in all and the daily dose should never exceed 0.2 gm. After the first course, the patient should rest for 6 to 8 weeks and then a second course should begin. The treatment is then continued by a series of 10 to 20 weekly injections of 0.1 to 0.05 gm. of the drug for one or two years.

2. *Sanocrysin.* (Sodium aurothiosulphate) is administered intravenously. The initial dose is 0.25 or 0.35 gm. The second dose should never exceed 0.65 to 0.75 gm. and is given 6 days after the first dose. The third and the fourth doses being 0.75 gm. each, the former given on the 12th day and the latter on the 19th day after the initial dose.

The patient should be in bed throughout the treatment. Toxic symptoms such as albuminuria due to damage of the kidneys, various cutaneous and ocular affections may appear in the course of the treatment. Slot and Deville (1934) used other organic gold preparations in acute and sub-acute rheumatism and rheumatoid arthritis cases. The preparations are solganal A, containing about 36.5 per cent. of gold and used as an intravenous injection, solganal B and solganal B oleosum, both are used as intramuscular injections; solganal B oleosum being an organic gold compound in an oily base. The use of an oily suspension increases the degree of tolerance resulting in gradual absorption with an even, prolonged effect. Solganal B oleosum was used in the majority of cases with encouraging results. The initial dose of solganal B is 0.01 or 0.05 gm. and is given every 4th day with an increased dose depending on the individual condition.

With solganal B oleosum, increase may be 0.1, 0.2, 0.3, 0.4, and 0.5 gm. respectively provided no reaction occurs. The average total dose is 2.5 gm. per series of injections but generally is between 1.0 to 1.5 gm. The majority of cases improved though pyrexia and jaundice appeared as complications in a few cases. Glucose was given by mouth to avoid toxic symptoms during and even some time after the treatment. The

cases were simultaneously treated with other anti-rheumatic drugs, colonic irrigation with normal saline and diet therapy.

Opothecrasy. The focal toxins have a deleterious effect on the general endocrine system of the body and are responsible for general dysfunctions of the glands. Of all the endocrines, the thyroid suffers most and this is evidenced by symptoms of hypothyroidism in some cases of chronic arthritis. To remedy this, thyroid extract is given by mouth along with measures to eradicate the septic foci. Iodine and its various preparations are also advocated. There are two obvious ways in which iodine may help the rheumatic patients. It may act indirectly by stimulating a defective thyroid and normalising its secretion both qualitatively and quantitatively. Another opportunity is afforded by the local accumulation of iodine near the inflammatory foci. Suitable conditions are thus provided to better the condition not only through the thyroid but by a direct action in the joints and the inflammatory foci themselves, whilst the storage and slow excretion of the drug ensure a steady uniform action throughout the system.

Histamine therapy. Deszo Deutsch (1931) recorded some results obtained by the use of histamine in muscular rheumatism. Compared with gold salts, the remedy is more natural and the action is clearly understood. In any irritation of the skin—chemical, thermal, electrical or mechanical—a substance is liberated which has been named 'H' by Lewis and Dale and it has a histamine-like action, dilating small vessels and thereby increasing the permeability and accelerating the circulation. Similar effects are obtained by physical therapy with massage, hot air baths, diathermy and other applications. But histamine has more powerful effects and these are more lasting ones—it may persist as long as ten hours after application. There are different methods of administration such as by local application or subcutaneous injection. The local form of treatment is favoured by Deutsch who applies blotting paper impregnated with histamine and attaches the anode of a constant current to this, making the patient hold the negative electrode in his hand. There is rapid reddening and heating of the skin under the pad; soon after, little white blebs appear which coalesce to form a patch of oedema. The patch increases in size even when the application is discontinued and disappears at the end of two hours without leaving any trace.

Another method is to apply histamine as a pomade which is massaged into the skin and then removed with ether. If a more intense reaction is desired, the skin is scarified first. Subcutaneous injection (0.5 mg.) of histamine hydrochloride has given good results. After such injections the face is flushed and a mild headache develops. The pain in the muscles and joints diminishes and subsequently the patient can do active and passive movements with greater ease and less pain. Jacchia advocates this method but holds that there is no effect unless the drug enters the circulation.

Histamine is of value only in the treatment of muscular and articular rheumatism, acute or subacute; it has no effect on tuberculous or syphilitic joints or on gouty or suppurative arthritis. Its effects are not in the nature of protein shock, it does not produce local antibodies, it is not an analgesic or sedative in its reaction except in as much as it improves and accelerates the circulation in the affected parts.

Histamine therapy is best avoided in the presence of marked hypotension or cardiac disease. If it is to be given in these cases, it is best given by ionisation, thus avoiding the slight histamine shock produced by the intradermal route. It appears to alleviate the pain of rheumatism. It will not take the place of salicylates, but it may succeed where they fail.

Surgical treatment. No surgical treatment is indicated in acute arthritis cases. Analgesics, local treatment with resting of joints, if necessary, with splints and other orthopaedic appliances are all that are needed at this stage. It is only in chronic cases and where deformities have appeared, surgical intervention is necessary to correct them and if possible to make them useful to patients so far as locomotion is concerned. Various surgical procedures such as synovectomy, arthrodesis, arthroplasty and other orthopaedic operations are necessary to correct such deformities.

ASCITES. Ascites means presence of free fluid in the peritoneal cavity. The peritoneum has remarkable power of absorption. Fluid substances are conveyed by the blood vessels, while insoluble bodies including micro-organisms are taken up by the endothelial cells lining the peritoneum, particularly on the under surface of the diaphragm. Normally the greater omentum secretes a certain amount of fluid in the peritoneal cavity. This is again absorbed. This secretion and absorption are so evenly balanced that there is just enough fluid to keep the serous surfaces moist and free from friction. In morbid conditions this state of equilibrium is disturbed and the amount of fluid may become excessive and this leads to ascites.

Collection of excess of fluid in the peritoneal cavity may depend on the passage of fluid in increased quantities into the sac, the rate of absorption failing to keep pace with this or completely stopping.

Increased secretion depends on changes in the endothelial cells of the peritoneum brought about by poisons; this process occurs in inflammation and is then spoken of as an exudation; or ascites may result from increased venous or lymphatic pressure—passive or mechanical effusion; the process is spoken of as a transudation. These two processes may overlap; thus passive venous engorgement, by interfering with the vitality of the endothelium, will produce changes analogous to those brought about by poisons.

The causes of ascites are:—(1) Backward pressure from tricuspid regurgitation or any other cause, (2) Chronic peritonitis (a) simple,

(b) dysenteric, (c) tuberculous, (d) malignant, etc. (3) Cirrhosis of the liver. (4) Other morbid conditions of the liver—perihepatitis, syphilis, lardaceous liver, malignant disease, lymphadenoma, etc. (5) Thrombosis of the portal vein. (6) Bright's disease. In addition, rupture of hydatid, ovarian or other cysts may give rise to free fluid in the peritoneal cavity. Rupture of lymphatic vessels or lacteals will cause chylous effusion, resembling true chylous ascites in appearance, but differing from it chemically are the two following forms:—(a) the chyloform or fatty, and (b) the milky non-fatty ascites. In chyloform or fatty (adipose) ascites the fat which is present in large globules is due to degenerative changes in cells suspended in ascitic fluid. In the milky (non-fatty) ascites there are a large number of mononuclear leucocytes which probably give rise, as a result of degeneration, to nucleo-albumin or globulin; this causes to the lactescent appearance of the fluid. No fat can be extracted by ether from the ascitic fluid in this form. Haemorrhagic ascites is sometimes met with. The causes are:—(1) rupture of ectopic gestation, (2) rupture of the spleen, (3) rupture of aneurysm, (4) new growth, (5) result of previous tapping, and (6) tuberculosis.

Characters of ascitic fluid. The characters vary according to the causes at work. Thus, when there is inflammation of the peritoneum (exudates) the specific gravity and amount of contained protein are higher than when ascites is associated with back pressure (transudates). Serous ascitic fluid is clear, transparent and greenish or faintly yellow in colour. The reaction is alkaline, and the specific gravity under 1012 in mechanical effusions or hydroperitoneum and 1018 or higher in exudations in sub-acute or chronic peritonitis. The amount of solids and proteins varies. In simple effusions due to renal disease there may be only 0.3 per cent. or less of protein, while in inflammation the amount may be 4 per cent. In jaundiced patients the fluid contains bile pigment. The cells seen on microscopical examination vary in different kinds of ascites. In ascites due to mechanical causes, e.g., heart disease and hepatic cirrhosis, endothelial cells are predominant, in tuberculous peritonitis small lymphocytes are present in high percentage and this is also found in the ascites due to intra-abdominal syphilis and malignant disease. In inflammatory conditions polymorphonuclear cells predominate in the ascitic fluid.

The ascitic fluid at the first tapping is usually sterile but as a result of paracentesis infection may occur. The colon bacillus and the tubercle bacillus are sometimes present

There may be a positive pressure inside the abdomen. Pitres found that it may vary between 30 and 6 mm. of mercury (average 12 mm.). This positive intra-abdominal pressure varies with respiration and is associated with increased pressure in the portal vein and low arterial pressure (Gilbert and Weil).

TREATMENT. The underlying cause should be looked for and treated adequately. The palliative treatment consists of measures towards removal of fluid. *Paracentesis.* It is indicated in the presence of any distress and pressure symptoms. *Diuretics.* Their use should not be persisted in when there are indications that paracentesis is necessary. They act well after paracentesis, which relieves the pressure on the renal veins. Good results have been obtained by injections of salyrgan intramuscularly or intravenously in conjunction with ammonium chloride and a salt-free diet.

Surgical measures (Talma Morrison's operation) have been advocated.

ASTHMA. The term 'asthma' derived from a Greek word meaning 'panting' is applied to a type of paroxysmal dyspnoea associated with prolonged expiration and wheezing respiration.

For purposes of treatment it can be classified into two main groups:—

1. *Secondary to infection or disease of the respiratory tract, i.e., nose, throat, trachea and bronchi.* This group includes a majority of cases amongst Indians.

(a) *Nasal reflex.* In this type the total leucocyte count is more or less normal, there is no eosinophilia, and the Arneth count is normal. The cases that respond favourably to aspirin will be benefited by a nasal operation. In such cases an examination of the nose and paranasal sinuses is carried out.

(b) *The cases in which the attacks are due to pressure of the enlarged hilus glands on the vagus nerve.* In such cases there is no increase in the number of total leucocytes or eosinophiles and the Arneth count is more or less normal. The X-ray picture will show enlarged hilus glands.

(c) *Bronchial cases due to infection in the bronchi.* These cases are subdivided into two groups. (i) Gram-negative bacilli cases. Total leucocyte count is high, there is marked eosinophilia and a shift in the Arneth count to the left. A smear of the sputum shows Gram-negative bacilli resembling pneumobacilli. The sputum is cultured and non-motile bacilli belonging to the Eberthella group are isolated. A vaccine is made from these organisms and is used for treatment. (ii) Bronchial cases in which the infection is due to the ordinary organisms causing bronchitis. Total leucocyte count may be high or low, there is no eosinophilia, but there is a marked shift in the Arneth count to the left. In such cases cultures from the sputum are made to get the strains for preparations of an autovaccine. An X-ray examination of the chest and a Von Pirquet's test should be done to exclude tuberculosis.

2. *The allergic cases.* These cases may be divided into three groups:

(a) *Local allergy of the mucous membrane to foreign substances such as dust.* These cases may be congenital or may be acquired as a result of the previous disease of the bronchi. The congenital cases are rare amongst Indians but common amongst Europeans. In India the condition is more often acquired as the result of previous bronchitis or may develop during the asthmatic state. This type is common amongst the jute workers and textile workers and in certain occupations where there is a large amount of dust in the atmosphere. The dermal tests are of value in diagnosing these cases. These can be treated with extract made from the dust; the treatment is carried out by giving graduated doses of the sterile dust extract.

(b) *Hereditary allergy, i.e., susceptibility to animal emanations, etc.* These cases are rare in India. Dermal tests are of value in the diagnosis of such cases. The treatment consists in avoiding the excitant or in desensitising against it.

(c) *Allergy due to internal toxins.* This can be subdivided into two groups, firstly it may be due to some rare or common food or foods. Dermal tests are useful in the diagnosis of these cases, but this type is rare amongst Indians. Secondly, allergic symptoms secondary to bowel diseases occur; these are much more common amongst Indians. The dermal tests are of no value, as either all the tests are negative or all the foods tested give positive results. These cases have to be treated along the lines laid down for treatment of allergy of alimentary origin.

There will be a number of cases which do not belong purely to one of the two groups—bronchial and allergic—but which are a mixture of the two types. For example if a case starts as a bronchial case but later the mucous membrane of the bronchi becomes hypersensitive to dust, etc., as a result of the disease, it will present a mixed blood picture, high leucocytosis, high eosinophiles and a marked shift in the Arneth count to the left. Similarly, in a case which starts as an abnormal sensitiveness of the mucous membrane to external stimuli the repeated turgescence of the membrane and its lowered resistance leads to bacterial infection of the mucous membrane and the bronchial glands may become enlarged due to this infection.

DIAGNOSIS. In an acute attack a detailed examination of the patient is hardly needed to make a diagnosis. The characteristic posture and the wheezing respiration are quite typical. The patient sits up with the back hunched, the sternum bulging out and the shoulders raised to the utmost. The skin is usually pale but may be a little cyanotic in patients with emphysema. The mouth is usually kept open to facilitate breathing. All the accessory muscles of respiration are straining to the utmost, and the sterno-mastoids are very prominent and tense. With all these violent efforts at breathing there is only slight movement in the chest. Percussion gives a hyper-resonant note and the area of cardiac dullness is much diminished. On auscultation, the

noisy râles and ronchi drown the respiratory murmur. The expiration is much prolonged and the inspiration is comparatively shortened

Clinically an asthmatic attack may simulate an attack of dyspnoea of cardiac and renal origin. The consideration of a few points will usually make the diagnosis clear. (1) In asthma the time of onset is usually in the early hours of the morning and the attacks are not associated with any physical effort. Cardiac dyspnoea is intimately associated with muscular effort and renal dyspnoea is often a pre-uræmic condition. (2) Difficulty in breathing of asthmatics is expiratory in type, while in cases of cardiac dyspnoea it is mostly inspiratory. (3) Asthmatics have usually got a low blood pressure, while in cases of cardiac and renal dyspnoea the blood pressure is high and there are evidences of heart disease and arteriosclerosis. (4) In renal and some cardiac cases the urine will contain albumin. There are some other conditions to be differentiated from asthma such as retropharyngeal abscess, pulmonary new growths, pathological states of the pleura, foreign body in the lung, aneurism, etc., but these offer no difficulty in diagnosis. In patients of advanced age the low type of pneumonia has to be specially kept in mind.

The personal and family history together with the results of the blood examination will usually enable a case of asthma to be classified into one of these two main groups. An examination of the nose and paranasal sinuses, a skiagram of the chest, Von Pirquet's test and sputum analysis will confirm the diagnosis in the cases in which the attacks are secondary to infection of the respiratory tract. The dermal tests and examination of the stool will help in the diagnosis of the allergic cases.

A history of the case is taken and the following points are carefully elicited. (a) A history of inheritance. This is commonly found in the allergic cases and rarely in the bronchial cases. (b) The pre-asthmatic state. A history of having suffered previously from pneumonia, chronic bronchitis or pleurisy is very suggestive of the bronchial type, while a history of a previous attack of dysentery or of urticaria is rather suggestive of the allergic type. (c) Age of onset, the seasonal variation of the disease and the association of the attacks with a certain place or food eaten are important points. A history of the disease starting after thirty years of age and the attacks coming on during the winter or rainy seasons or being worse at these seasons is characteristic of bronchial cases. In these cases there is no association of the attack with any place or food. The allergic cases usually start early in life, have no seasonal variation and the attacks may show an association with some place or food.

Examination of the blood. Total and differential count of leucocytes are done and the total number of eosinophiles per cubic millimetre of blood is calculated. An Arneth count is done along with the differential count.

The total number of leucocytes is not of much value owing to various diseases in the tropics, such as malaria and kala-azar, lowering the count. A high count is suggestive of sepsis and is found in bronchial cases, but when the high count is due to an increase in the number of eosinophiles it is found in the allergic and the Gram-negative bacilli cases.

The number of eosinophiles. Sometimes the results are difficult to interpret owing to other causes depressing the bone-marrow such as kala-azar or malaria. A point to realise is that the results expressed as percentages of eosinophiles are not of much value, because a 5 per cent. eosinophilia with a total count of 5,000 leucocytes only means 250 eosinophiles per c.mm., with a count of 10,000 there are 500 eosinophiles per c.mm., and with a count of 20,000 there are 1,000. It is better to express the results in terms of total eosinophiles per cubic millimetre of the blood. Roughly an eosinophile count of over 1,000 per cubic millimetre is suggestive of allergy, but is also seen in the Gram-negative bacilli type.

The Arneth count, which is a count of the polymorphonuclear cells according to their maturity, is of great diagnostic value. The young forms have one-lobed nuclei, and the number of the lobes increases with increasing age of the cells. In bronchial cases where sepsis is present there is an increased demand on the bone-marrow so that young forms are thrown into circulation at a greater speed than normally. The result of this enhanced supply is that when an Arneth count is made the number of cells with one or two-lobed nuclei is found to be greater than normal. This is spoken of as a shift to the left in the Arneth count. The Arneth index, which is the sum of the cells with one and two-lobed nuclei and half the cells with three-lobed nuclei naturally rises with this left-handed shift in the count. An Arneth index above 70 is suggestive of bronchial cases. In the allergic cases there is no sepsis and hence no demand on the bone-marrow for the increased production of the polymorphonuclear cells so that the Arneth count and the Arneth index are more or less normal in these cases. An Arneth index below 70 is suggestive of allergic cases. It is to be noted that in allergic cases with leucocytosis, although the bone-marrow is active, there is no left-handed shift in the Arneth count, because the increase in the number of the leucocytes is due to an increase in the number of eosinophiles and not of the polymorphonuclear cells.

It can be concluded that the bronchial cases usually have an Arneth index above 70 and an eosinophile count below 1,000 and the mixed bronchial and allergic cases have an Arneth index above 70 with usually an eosinophile count of above 1,000. The Gram-negative bacilli cases usually have an Arneth index above 70 with an eosinophile count of above 1,000, while in the allergic cases the Arneth count is almost always below 70 and this is usually associated with an eosinophilia of

above 1,000, but the eosinophile count may be low in some cases when the total count is low.

Analysis of the sputum. A smear made from the purulent portion of the sputum shows the common micro-organisms—pneumococci, streptococci and micrococcus catarrhalis. In about one-fifth of cases in addition to these micro-organisms Gram-negative bacilli resembling *Klebsiella pneumoniae* (Friedlander) are found. Special significance has been attached to the presence of these bacilli in the sputum. Knott and Oriel (1930) obtained a histamine-like effect with extracts of various asthmatic sputa. Referring back to the bacteriology of these particular sputa, they found that many showed numerous Gram-negative bacilli in the bronchial plugs. The broth culture of these bacilli cause a histamine-like effect similar to that obtained from the sputum. They think that the histamine-like substance demonstrable in the plugs has arisen as a result of the growth of these bacilli within the small bronchial tubes. Oriel (1932) considers that the local production of histamine in the bronchi in addition to causing contraction of the plain muscle surrounding the bronchi, would also tend to increase the permeability of the epithelium lining the bronchioles and facilitate the entrance of foreign proteins and possibly bacteria. The Gram-negative bacilli cases constitute a clinical group characterised by a high blood eosinophilia and the presence of pleomorphic Gram-negative bacilli in smears and cultures of the sputum. The benefit derived in these cases from vaccines made from these bacilli is the same as in the other bronchial cases.

The presence or absence of eosinophiles in the sputum is not of any diagnostic value.

Therapeutic test. During the attack of asthma, the effects of atropine, aspirin and adrenalin are tried in turn, beginning with the atropine, then aspirin and finally adrenalin. In some severe cases none of these three drugs gives any relief to the patient and we have to give morphine-atropine injection. *Atropine*—a subcutaneous injection of 1/150th gr. of atropine sulphate is given at the onset of the attack. Atropine paralyses the vagal nerve-endings in the bronchi and if the attack is due to broncho-constriction due to reflex stimulation of the vagus the injection will relieve the patient. On the other hand, if the attack is due to direct chemical stimulation of the bronchial muscles it will have no effect on the attack.

Aspirin is given in form of an A. P. C. powder (aspirin 5 gr., phenacetin 3 gr. and caffeine citrate 5 gr.). In the bronchial cases it is a very effective drug and relieves the spasms. In cases where the broncho-constriction is due to direct chemical stimulation, i.e., in the allergic cases, the drug has no effect.

An injection of 0.3 to 0.5 c. cm. of adrenalin hydrochloride (1 in 1,000 solution) is given subcutaneously at the onset of the disease.

The allergic cases are benefited by this injection more than the bronchial cases. Adrenalin has no action on the vagus nerve-endings and will act best when the broncho-spasm is due to direct chemical stimulation.

The diagnosis can then be further confirmed. In the cases due to infection in the respiratory tract the nose and the paranasal sinuses are examined. A Von Pirquet's test is done and a skiagram of the chest is taken. The Von Pirquet's test and an X-ray picture are of value in excluding tuberculous lesions of the lung.

The diagnosis in the allergic cases is confirmed by the examination of the stools and the results of the dermal tests.

Examination of the stools. The allergic cases secondary to gut infections may show *Entamoeba histolytica* infection or the presence of the ova of various helminths. The McConkey neutral-red lactose agar plate may show various non-lactose-fermenting bacilli causing post-dysenteric lesions. These findings are rather important from the treatment point of view. These cases of gut origin are treated with emetine, carbon tetrachloride or an autogenous vaccine prepared from the pathogenic organisms isolated from the stools depending on whether the case is one of amoebic infection, hookworm disease or some post-dysenteric lesions of the gut. In the ordinary way these infections do not cause asthma, but there may be a lowering of the defence mechanism of the liver caused by amoebic or some other form of hepatitis.

The dermal tests are of value in the following cases. (1) When the respiratory mucous membrane is locally sensitive to dust, such as in case of jute workers. (2) In cases who are sensitive to animal emanations. (3) In cases in whom a single rare food is responsible for the attacks.

In the allergic cases dependent on some pathological condition of the gut the dermal tests are no good; the tests are either negative in all the cases or all the foods tested give a positive result. The dermal tests should be done only when the history is suggestive of some animal emanation or some particular food being responsible for the attacks.

TREATMENT. This can be considered under two general headings—the management of the asthmatic attack and the treatment of the asthmatic state.

Management of the asthmatic attack. Medicinal treatment. Previous experience of the patient is usually sufficient to tell which of the drugs, atropine, A. P. C. powder or adrenalin, will prove most beneficial to him. When none of these acts a morphine-atropine injection is to be given.

A subcutaneous injection of 1/150th gr. of atropine is given at the onset of the attack. The patient will be relieved if the attack is due to a broncho-constriction brought about by reflex stimulation of the vagus. The drug is contra-indicated in the presence of emphysema. The dryness it produces is a drawback, because thereby it may increase the cough.

A powder consisting of aspirin, phenacetin and caffeine citrate effectively controls the attacks in the bronchial cases. Aspirin sensitivity is, however, to be kept in mind, because this is the commonest form of drug hypersensitiveness to be seen amongst the allergics.

Adrenalin must always be given intramuscularly. It is of no value when given orally, because it is inactivated by gastric and intestinal secretions. An intracutaneous injection of adrenalin is very painful and the effects of its intravenous injection are very unpleasant. Violent headaches, severe vertigo, palpitation, tremor, breathlessness, precordial pain, nausea and vomiting may result if adrenalin enters into a vein. Adrenalin acts by stimulating the sympathetic nervous system and by shrinking the oedematous mucous membrane lining the bronchioles. The smallest effective dose of the drug should always be employed so that relief is obtained without unpleasant by-effects. The earlier the injection is given the smaller will be the dose required. Three to six minims given at the beginning of an attack will usually control the symptoms whereas large doses late in the paroxysm may fail to do so. For this reason many workers advocate teaching the patient the use of a hypodermic syringe so that he can get the benefit of small doses of the drug at the outset of the attack. It is quite safe to do this, because adrenalin is not a habit-forming drug. With frequent administrations an increase in dosage may be needed, as there is a rapidly acquired tolerance to the drug.

Hurst advocates a continuous method of adrenalin injection in *status asthmaticus* where severe asthma has continued uninterruptedly for days or weeks. The needle of the syringe is kept constantly in position and after the initial injection of a dose that is known not to cause unpleasant symptoms, one or more minims are injected every fifteen, thirty, or sixty seconds according to the patient's reactions, the rate being varied until it is found how frequently the injection can be made without any unpleasant symptoms arising. The injections are carried on for half an hour or so if necessary. Ephedrine, a drug prepared from the stems of *Ephedra vulgaris*, has the same effect of stimulating the sympathetic nerve-endings as adrenalin. Ephedrine can be used in place of adrenalin, but it is of use only in mild cases or as a preventive. Ephedrine can be given orally and its effect is prolonged for several hours, though it is not so prompt in action as adrenalin. The sulphate and hydrochloride of ephedrine are available. Dosage for an adult is 3/8 to 3/4 gr., 1/8th gr. for a child under one year of age and 1/4th gr. above one year. Ephedrine may also be given subcutaneously, but this has got no advantage over a subcutaneous injection of adrenalin.

Besides ephedrine, pseudo-ephedrine, another alkaloid obtained from ephedra has been used in these conditions. Chopra and his co-workers (1931) state that the broncho-dilator action of the drug appears to be quite as marked as that of ephedrine without the unpleasant side effects of the latter. The alkaloid should be given in doses of 1/2 gr.;

the effect is noticed within fifteen minutes to half an hour of oral administration. A similar dose taken when the premonitions of an attack are felt, generally stops the paroxysm, and it can therefore be used in all cases where ephedrine is employed.

Morphine is a valuable drug for controlling a severe attack when other measures have failed. It should be used only as a last resort in asthma and should be combined with atropine.

A mixture containing potassium iodide and antispasmodics such as lobelia, stramonium, belladonna and kuth is given during and between attacks. Iodides liquefy the bronchial secretions and make the cough more effective.

General treatment of the attack. A good purgative is given in the beginning and then the bowels are kept open by mild saline laxatives. A loaded sluggish bowel tends to retard recovery, hence it is essential that the patient should not be allowed to remain constipated. In patients with a distended stomach an emetic affords great relief. It relieves the stomach distension and loosens the mucus in the lungs. In children emesis may be induced by tickling the throat. Taking a large dose of sodium bicarbonate or ordinary salt in a glass of water also serves the same purpose. Large doses of vinum ipecacuanha or a hypodermic injection of 1/20 to 1/10 gr. apomorphine hydrochloride may have to be used.

No food should be given for twenty-four hours, plenty of water and hot weak tea should be allowed in this period. In cases of exhaustion stimulants are indicated. With the subsidence of symptoms a simple, soft, and easily digested diet should be allowed. The patient should be allowed to choose those simple foods which he has by experience found to be harmless.

Treatment of asthmatic state. Treatment between the attacks has for the most part been indicated while describing the types of asthma. A few additional remarks are however needed. The patient should be thoroughly overhauled and any infective focus found or any endocrine dysfunction discerned should be adequately treated. The results with endocrine therapy are encouraging only in a limited number of cases, still it is worth trying wherever indicated. The suprarenals, the thyroid and the sex glands are most commonly involved. The desiccated glands may be given by mouth. Injections of arsenical preparations such as soamine are used to tone up the endocrine system.

The allergic cases, in which no definite offending cause is found, may be treated by means of non-specific desensitisation as described under treatment of allergy.

(8) Gastric distension commonly precipitates an attack, so that late and heavy meals should be avoided. To avoid flatulent dyspepsia the food should be thoroughly masticated and any errors in gastric secretion should be corrected. For hypochlorhydria administration of hydro-

chloric acid by mouth may suffice or a daily gastric lavage may have to be done to treat the underlying chronic gastritis.

In cases of hypochlorhydria Bray recommends $\frac{1}{4}$ to 2 dr. of dilute hydrochloric acid in a cup of orange or lemon juice three times a day before or with meals. For children he recommends pepsin 1 gr., dilute hydrochloric acid 30 min., pure dextrose 30 gr., syrup of senna 10 min., in two ounces of chloroform water. Two teaspoonfuls of this mixture are to be given in orange or lemon juice three times a day. Constipation should at the same time be well guarded against.

Potassium iodide mixture along with antispasmodics such as lobelia, stramonium, belladonna, tincture ephedra and kuth is regularly given for some time. It is usual to add arsenical solution to the mixture. Arsenic is said to have a favourable influence on bronchitis and asthma when given over long periods. Bray recommends the following mixture for children:—Potassium iodide 2 gr., arsenical solution 1 min., tincture of stramonium 3 min., with 10 min. of syrup. Patients suffering from irritating nocturnal cough derive benefit from a dose of linctus at bedtime; linctus paregoric may be used or the following may be given: tinct. of stramonium 15 min., syrup pruni verg. 1 dr., and syrup codeine phosphate 1 dr.

A passing reference may here be made to asthma powders, cigarettes, sprays, etc. Stramonium leaf is the main constituent of most asthma powders and cigarettes, it is mixed with saltpetre to aid its combustion. In some patients these act as preventives and help to cut short mild attacks, but to many patients the fumes are annoying, irritate the mucous membranes of eyes, nose, and throat and induce severe cough. Most sprays contain either atropine in some form, cocaine or adrenaline, some chronic asthmatics get transitory relief from these sprays. Powders, cigarettes and sprays have no place in the treatment of acute attacks.

Breathing exercises are essential, specially to remedy any deformity of the chest which might have resulted from the repeated attacks. The patient is in the habit of using the upper part of his chest for respiration and the exercises are designed to teach him to use the lower part of his chest and the diaphragm.

BATHS. See page 118.

BED SORES. See page 1499.

BERI-BERI. See page 1018.

BLACKWATER FEVER. (See page 574). *Investigation*:—(1) Repeated examinations of thick and thin films of blood for malarial parasites and culture if possible. (2) Examination of urine for hæmoglobin and methæmoglobin spectroscopically and chemically; also for urobilin, albumin and casts. (3) Van den Bergh test of serum. (4) Determination of the cell volume and size of the red blood cells. (5) Fragility of red blood cells. (6) Blood count.

When it is noted that the patient is suffering from oxyhæmoglobinuria without cyanosis a diagnosis of blackwater fever is probable. When there is methæmoglobinuria with cyanosis, plasmoquin toxicity is suggested.

TREATMENT. Careful nursing and administration of plenty of fluids are important. Urine is measured and its character noted each time.

(1) Pituitrin and adrenalin injections, repeated if necessary after 12 hours in collapsed and exhausted cases. (2) Calcium lactate 10 gr. and parathyroid extract 1/10 gr. twice daily. (3) Alkaline mixture every 4 hours. (4) Intravenous glucose and sodium bicarbonate if there is any tendency towards suppression of urine. (5) Blood transfusion if required. (6) Atebrin, a full course if malarial parasites are found. During convalescence, treat the anæmia with iron, arsenic and in the macrocytic type with liver preparations. For further detail see page 574.

BLOOD IN HEALTH AND DISEASE.

Composition of blood. Blood contains plasma and cellular elements. Plasma includes serum and fibrinogen which yields fibrin on clotting. Serum contains serum albumin, serum globulin, glucose, extractions, calcium salts, sodium and potassium chlorides, carbonates, phosphates, etc. The cellular elements consist of red cells, white cells (fibrin ferment), blood platelets, hæmoconin. The red cells contain oxyhæmoglobin, lecithin, and salts. (Webster and Koch).

The blood volume. In adults the blood volume is 5 to 5½ litres (10 to 11 pints) or one-fifteenth to one-thirteenth of the body weight. Blood volume is increased in pregnancy just before term, hypertensive and in anasarca accompanying cardiac insufficiency. Decreased total volume occurs when there is excessive loss of fluid as in polyuria, diarrhoea, profuse sweating, etc. A loss of 350 c.cm. of blood in an adult has no appreciable effect on the blood pressure; with the next 350 c.cm. loss, a slight but definite depressor effect results; if the loss reaches 1,750 c.cm. the fall of blood pressure is very marked.

Viscosity of the blood. The viscosity of blood is compared with that of water on the principle that fluids at equal temperature and pressure passing through tubes of equal calibre vary in their rate of flow in direct proportion to their internal friction. The apparatus of Hess is generally used for determining viscosity of blood. Normal viscosity of blood varies from 4.3 to 5.3 for males and 3.9 to 4.9 for females, and of serum from 1.7 to 2 for both sexes.

* The viscosity of blood depends on : (1) the cell volume; an increased cell volume increases the viscosity and white cells are more viscid than red cells; (2) the hæmoglobin content; an increased hæmoglobin content causes an increase in viscosity; cyanosis increases the viscosity

and venous blood is more viscid than arterial; (3) the protein content; dehydration by increasing the protein content increases viscosity. General cedema or anæmia which lowers the protein content also lowers the viscosity of blood. In profuse perspiration in health, the viscosity of blood is considerably increased. The viscosity is also increased in severe types of pneumonia, in diarrhœas and in some protracted types of vomiting. With an increase of cell content per unit volume of blood, the viscosity of blood is increased and a greater load is thrown on the heart. The cell concentration and viscosity give optimum efficiency with the minimal heart work when the cell volume lies between 40 and 50 per cent. of the blood volume.

PHYSICAL AND CHEMICAL CHARACTER. (Values are in mg. per 100 c.cm. whole blood unless otherwise noted.)

Specific gravity	...	1,056 to 1,066 (1.028 to 1.032 for serum, 1,090 for corpuscles).
Reaction	...	pH 7.3 to 7.4
Total solids	...	19 to 23 per cent.
Hæmoglobin	...	14 per cent. (by weight).
Serum albumin	...	4.6 to 5.3 per cent.
Serum globulin	...	1.8 to 2.7 per cent.
Fibrin	...	0.2 per cent.
Total nitrogen	...	2.6 to 3.5 per cent. (plasma, 0.6 to 1.1)
Nonprotein nitrogen	...	25 to 35 (plasma, 20 to 35)
Urea	...	20 to 40
Urea nitrogen	...	12 to 15 (plasma, 10 to 23)
Amino-acid nitrogen	...	6 to 8 (plasma, 4 to 7)
Ammonia nitrogen	...	about 0.1
Uric acid (Folin-Wu method)	...	2 to 3 (extremes, 1 to 3.5) (plasma, 2.5 to 5)
Creatinine	...	1 to 2 (plasma, 0.8 to 1.5)
Creatine	...	3 to 5 (plasma, 0 to 3.8)
Sugar (Folin-Wu method)	...	90 to 120 (same for plasma)
Chlorides (as NaCl)	...	450 to 500 (plasma, 570 to 620)
Fat (Bloor's fat method)	...	about 600
Cholesterol (Bloor's method)	...	140 to 170
Lecithin (Bloor's method)	...	30 (plasma, 22)
Acetone bodies	...	0 to 4
Bicarbonate (plasma)	...	53 to 77 vol. per cent. CO ₂
Oxygen capacity	...	18.5 vol. per cent.
CO ₂ tension (arterial)	...	about 40 mm. Hg.
Calcium	...	5.3 to 6.8 (serum or plasma, 9.0 to 11.0)
Magnesium	...	2.3 to 4 (serum or plasma, 1.6 to 3.5)
Sodium	...	170 to 225 (serum or plasma, 335)
Potassium	...	153 to 240 (serum or plasma, 18 to 21)
Phosphorus, total (as H ₃ PO ₄)	...	about 120 (plasma 35 to 40)
Phosphates, inorganic (as P)	...	(serum) 3.2 to 4.3
Sulphates (as S)	...	0.5 to 1.0 "
Bilirubin	...	0.1 to 0.25

NORMAL CELLS OF THE BLOOD

WHITE BLOOD CELLS.

Total number	5,500 to 8,500 per c.cm.
Polymorphonuclear				
Neutrophile	60 to 75 per cent.	
Eosinophile	...	1 to 7	,, ,,	
Basophile	...	0 to 1	,, ,,	
Mononuclear				
Monocytes	...	2 to 7	,, ,,	
Lymphocytes	...	25 to 30	,, ,,	

(1) *The polymorphonuclear leucocyte.* This cell is about 10μ in diameter and has an irregularly shaped and lobed nucleus. The cytoplasm stains a very faint blue and is thickly dusted with fine, faintly pink-staining neutrophile granules.

(2) *The small lymphocyte.* This cell is about the same diameter as the red corpuscle. It has a rounded or spherical nucleus which stains most intense purple and occupies almost the entire cell, leaving around it only a narrow rim of rather deeply blue-staining cytoplasm.

(3) *The large lymphocyte.* This resembles the small lymphocyte but is larger. It has a round or sometimes oval nucleus which stains very deeply and a considerable volume of rather pale blue-staining cytoplasm which frequently shows a few purple-staining granules. The largest of these cells which are up to 12μ in diameter are equal to the polymorphonuclears. This point serves to differentiate them from monocytes which are larger.

(4) *The large hyaline mononuclear leucocyte.* The cell has a diameter of about 14μ and is about one and a half or twice the size of the small lymphocyte. The nucleus is large, oval, eccentric in position in the cell and much looser than the nucleus of the lymphocyte. The nucleus stains much less intensely than does the nucleus of the lymphocyte, and it is indented, notched or partly bilobed. The volume of cytoplasm is considerable and often contains a few scanty azure pink-staining granules.

(5) *The coarsely granular eosinophile leucocyte.* It is about 12μ in diameter, and the nucleus is bilobed, or very occasionally trilobed. Frequently the nucleus consists of two more or less spherical masses of chromatin connected together by a thin strand of chromatin. The cytoplasm of the cell is full of large deeply brick-red-staining granules.

(6) *The transitional mononuclear leucocyte.* The cell resembles the large hyaline mononuclear leucocyte but the nucleus is more indented and not unlike that of the polymorphonuclear leucocyte. The nucleus is horse-shoe-shaped and takes a washed-out violet shade of less intensity than that of the large hyaline mononuclear. For practical purposes the transitional leucocyte may be included with the large hyaline mononuclear leucocyte.

(7) *The finely granular basophile leucocyte.* This is a very rare type of cell. It has a frayed out, bilobed or trilobed nucleus and its cytoplasm is dusted with very small fine granules which take a blue stain.

(8) *The mast cell.* This is coarsely granular basophile cell. It is about the size of a polymorphonuclear leucocyte, and has a bilobed, sometimes trilobed, nucleus. Its cytoplasm contains numerous large granules which stain a deep blue to black colour.

Leucocyte count. Capillary blood from the fingers is generally made use of in the total count of white blood cells. A large drop of blood is required for the purpose. The blood is sucked into the pipette up to the mark 0.5 and the same is diluted with W.B.C. fluid (glacial, acetic acid 38 min., mercuric chloride 1.5 gr., and water to 4 oz.) up to the mark 101. The pipette containing the fluid is shaken well. The Thoma-Zeiss type of counting chamber is used which has a rounded disc on which the ruled lines are cut. This surface is exactly $1/10$ mm. below the general surface and is surrounded by a deep channel. The blood drop should be put over it so as just to cover the ruled area only and it should not flow into the channel around. For a leucocyte count the whole central ruled area containing 1 sq. mm. is used. After placing the drop of blood on the counting chamber, one minute should be allowed to elapse for the cells to settle. All the cells contained in the 16 squares should be counted. The corpuscles touching the upper and left side lines of the squares should be counted while those touching the lower and right sides should not come in the count. Multiply the total of the cells by 312. Repeat the count and take the average of both counts. This is the number of cells per cubic millimeter. The new type of counting chamber with Neubauer ruling has got a distinct advantage over the Thoma-Zeiss type. There is less chance of overflow. This type facilitates the counting of four squares in one preparation. The total count of the cells in the four squares multiplied by 50 gives the number of leucocytes per cubic millimeter.

Oxalated venous blood has a decided advantage where the examination is not done at the bedside, and the blood has to be sent to a distant place. The bottle should be well shaken before counting. The pipette is most easily filled from a large drop put on a glass slide.

Differential count of white blood cells. A small drop of blood from a punctured finger is placed near one end of a glass slide and with another slide or some other spreader it is spread evenly over the glass slide. The smear should not be very thin. *Stains used.* (1) Eosin and hæmatoxylin. The slide is immersed in the vial containing the alcoholic solution of eosin for one to two minutes; this is thoroughly washed with water. The slide is then immersed in the other vial containing hæmatoxylin, for three to five minutes. It is again washed with water and then dried. (2) 'Wrights' or Leishman's stain. About 10 to 15 drops of the stain are put over the glass slide

and kept for two minutes. The stain is then diluted by adding distilled water and is left for 3 to 5 minutes. The whole is then washed off by flooding with water and then dried. The differential count is done under an oil-immersion lens of the microscope, 200 white cells being counted and recorded by a tally system. The percentage of each variety is then calculated.

LEUCOCYTOSIS. Any increase in the leucocyte count to over 10,000 per c.mm. is considered a leucocytosis whether such an increase is due to a physiological or a pathological cause.

I. *Physiologic leucocytosis.* (a) In the new-born the average count is 20,000 per c.mm. and as many as 25,000 per c.mm. are recorded. During the first and second days of life the count falls but again rises by the end of the first week to 10,000. (b) In later weeks of pregnancy and during labour the count rises to over 30,000 per c.mm. (c) After exercise, convulsions or severe massage to about 12,000 per c. mm. (d) Digestive or alimentary leucocytosis. *Hæmoclastic test.* If the proteopexic function of the liver is impaired, a protein meal will be followed by a reduction in the white cell count instead of by the usual digestive leucocytosis. (e) From altered circulation. Slight increase in the leucocyte count results from slowing of the blood stream or stasis. Posture, vasomotor influences and changes in temperature slightly alter the count.

II. *Pathological leucocytosis* is characterised by an altered ratio of all the types. Generally the increased count is due to an increase in the neutrophilic granular leucocytes. Such leucocytosis commonly occurs from infection by pyogenic cocci, as in inflammatory conditions, viz., pneumonia, appendicitis, cellulitis, etc. Pertussis is marked by an increased number of lymphocytes.

Leucocytosis is marked after the use of extracts from highly cellular organs, adrenalin, nuclein, turpentine, camphor, antipyrine, phenacetin, digitalis, pyrogallol, salvarsan, and after long continued chloroform narcosis.

Leucocytosis is also marked in uræmia, eclampsia, acidosis, intestinal obstruction, burns, and occasionally rickets. Even toxic food or excess of alcoholic beverages may cause a temporary increase in the leucocytes. Leucocytosis is also the characteristic feature in leukaemia.

Post-hæmorrhagic leucocytosis is more marked when bleeding occurs in a serous sac or into a joint cavity and as many as 20 to 30 thousand per c.mm. are recorded. In neoplastic conditions, leucocytosis is more marked when metastasis in bone-marrow takes place in cases of sarcoma and carcinoma, and as many as over 40,000 per c. mm. have been recorded.

EOSINOPHILIA. I. *Physiological.* In infancy, up to 10 per cent. (in Indians.)

II. *Allergic.* (a) Bronchial asthma, often slight, occasionally as high as 20 per cent of 20,000. (b) Hay fever, up to 10 per cent. during the

period of symptoms. (c) Migraine, inconstant and slight. (d) Urticaria, eczema and with positive tuberculin reaction.

III. *With parasitic infestations.* (Possibly only another manifestation of allergy). (a) Infection with intestinal tænia (not constant), ankylostomes (up to 15 per cent. of 10,000), ascariis, oxyuris, etc. (far less constant) amœbic dysentery (inconstant). (b) In tissues: trichina; (20 per cent. of 20,000 and higher), echinococcus (50 per cent. of normal total count), coccidioidal granuloma (occasionally high, 12 per cent. of 22,000), filaria (less marked, occasionally 15 per cent.) and bilharzia.

IV. *Familial eosinophilia* is high and persisting but rare.

V. *In skin diseases.* Angioneurotic œdema (variable, up to 85 per cent. of 44,000), pemphigus (up to 60 per cent.), Dühring's disease (up to 40 per cent. of 12,000), scabies (5 to 15 per cent.), herpes zoster (occasionally high), psoriasis, urticaria, eczema (less marked).

VI. *In diseases of the hæmopoietic system.* Myelocytic leukæmia (1 to 5 per cent. of high total count), the so-called "eosinophilic leukæmia" (80 per cent. of 100,000). Hodgkin's disease (usually trifling, occasionally as high as 55 per cent. of 25,000).

VII. *With certain infections.* (a) Cholera (4 to 16 per cent. of normal total count, gonorrhœa (inconstant, may be up to 12 per cent.), scarlet fever (5 to 10 per cent. of 20,000), and active tuberculosis. (b) Post febrile, e.g., after pneumonia (up to 13 per cent.), measles, varicella, rheumatic fever and malaria (only slight).

VIII. *In certain diseases of bone.* Sarcoma, metastatic carcinoma, osteomyelitis, rachitis, osteomalacia, osteitis deformans.

IX. *With various neoplasms.* Rare but reported up to 30 per cent.

X. *In endocrine disorders.* Addison's disease (6 to 10 per cent.), ovarian disease (non-suppurative, non-malignant), also reported with menstruation.

XI. *From certain chemicals, etc.* After administration of uncooked liver (up to 50 per cent.), following camphor, pilocarpin, phosphorus, chronic copper sulphate poisoning, etc.

XII. *After irradiation.* Two to three weeks later (up to 20 per cent.).

XIII. *After splenectomy.* After 1 month (up to 15 per cent. for many months).

LYMPHOCYTOSIS. In children from the first two weeks of life up to five years the lymphocyte percentage is 40 to 70. Conditions usually accompanied by lymphocytosis are:—(1) Pertussis. The average mature lymphocytes often constitute 60 or more per cent. The maximum count is about 80 per cent. during the second week of the disease. (2) Infectious mononucleosis. The average lymphocytic count is about 70 to 80 per cent. of the total count. (3) Malta fever. (4) Chronic lymphocytic leukæmia. The lymphocytes usually constitute from 90 to 99 per cent. of the total count. (5) Certain aleukæmic lymphadenoses. (6) Mycosis fungoides with leukæmic blood changes. (7) Certain disorders of the

ductless glands. (8) Certain neoplasms particularly in connection with growths of lymphatic tissues as lymphosarcoma where as much as 90 per cent. of the total count are lymphocytes. (9) Syphilis. (10) Typhoid fever (relative only). (11) Tuberculosis (relative only). (12) Ricketts (relative only).

MONOCYTOSIS. This is marked in infectious mononucleosis, tetrachlorethane poisoning, subacute bacterial endocarditis, some forms of septicæmia, Hodgkin's disease, kala-azar, occasionally in typhoid fever, malaria (in some chronic cases during the afebrile intermissions), during the subsidence of the acute stage of acute infections and in rapidly advancing tuberculosis, syphilis (dementia paralytica), and monocytic leukemia.

POLYMORPHONUCLEAR LEUCOCYTOSIS. Leucocytosis due to polymorphonuclear neutrophil increase is usually due to infection by cocci of some variety. Non-infectious tissue lesions may also cause it.

In bacterial infection over 85 per cent. of polymorphonuclears points to pus formation; 90 per cent., to very severe infection. The resistance is good if the total leucocytes are increased proportionally and poor if they are not increased. There should be

15,000 total with 80 per cent. polymorphonuclears.

20,000 total with 85 " "

25,000 total with 90 " "

Pneumococcal infections give very high figures especially in the total counts.

ARNETH COUNT. Polymorphonuclear leucocytes have a life in the blood stream, of about three weeks. When a cell first enters the circulation its nucleus has only one lobe, but the nucleus gradually becomes more segmented, developing five lobes in the oldest cells. In health the proportion of cells respectively with 1-, 2-, 3-, 4-, and 5-lobed nuclei is fairly constant; a variation occurs in microbic infections when more young cells (1 to 2 lobes) are seen.

ARNETH INDEX. Arneth divided the polymorphonuclears under 5 classes according to the number of nuclei or nuclear fragments.

A polymorph with one nucleus belong to class I.

A " " two nuclei " " " II.

A " " three " " " " III.

A " " four " " " " IV.

A " " five or more nuclei belongs to class V.

The sum total of classes I and II is the Arneth index.

The following are the normal figures:—

Class	I	II	III	IV	V	Index.
	5	35	41	17	2	40

If the index is more than 40 the picture is said to be a "drift or shift to the left"; if less than 40, "shift to the right." A shift to the

left takes place in most of the infections. A shift to the right takes place in leprosy, syphilis, etc.

The index or hæmogram proposed by *Schilling* is simpler and has come into vogue recently. In this classification four types are recognised. 1. *Myelocytes* with single round nucleus. 2. *Young metamyelocytes*, which has a plump nucleus. 3. *Older metamyelocytes* with deeply indented nucleus but no true lobulation. 4. *Polymorphonuclears*. In *Schilling's* method each variety of neutrophilic granular cell is counted separately and expressed as a percentage of the total leucocyte count. According to *Schilling* the following is a normal count: Total leucocytes, 6,000 to 8,000; Neutrophilic granular cells 67 per cent. which are divided as follows:—Polymorphonuclears 63 per cent.; old metamyelocytes 4 per cent.; old metamyelocytes, absent; eosinophiles, 8 per cent.; basophiles 1 per cent., lymphocytes 23 per cent.; monocytes 6 per cent. This method advocated by *Schilling* indicates the age of the cells and there is no difficulty in recognising the various types of cells.

LEUCOPENIA. In disease a count below 5,000 is considered a leucopenia and it occurs in the following conditions. (1) Infections, *e.g.*, typhoid and para-typhoid fevers, and briefly after typhoid vaccination, influenza (except at onset), malaria, kala-azar, measles and rubella, small pox (up to fourth day), dengue, pappataci fever and overwhelming infections. (2) Intoxications, *e.g.*, benzol, arsenic, antimony, lead, irradiation with Roentgen ray and radium, early stage of reaction to parenteral foreign protein, inanition. (3) Diseases of the hæmopoietic system, *e.g.*, aplastic Addisonian anæmia, Banti's disease, primary leucopenia (agranulocytic angina), Gaucher's disease and the aleukæmic stage of leukaemia.

ABNORMAL LEUCOCYTES. The *myeloblasts* are the parent cells of the myelocytes, and are characteristic of the blood in spleno-medullary leukaemia. The size of the cell resembles the large lymphocytes with a round nucleus which stains intensely. The nucleus frequently shows three or four nucleoli within it. The cytoplasm is non-granular and intensely basophile. The *neutrophile myelocyte*, the parent cell of the polymorphonuclear leucocyte, is seen in enormous numbers in blood films from cases of spleno-medullary leukaemia, and occasionally in malarial cachexia. The cell is about 15μ to 20μ in diameter and the nucleus is rounded or may be indented or horse-shoe shaped. The cytoplasm contains tiny neutrophile granules staining a faint pink. The *eosinophile myelocyte* is the parent cell of the coarsely granular eosinophile and is met with in spleno-medullary leukaemia. The nucleus is central in position and rounded and the cytoplasm stuffed with large deeply brick-red-staining granules. The *basophile myelocytes* are believed to have been derived from the connective tissues and not from the bone marrow. The cells contain a relatively small round nucleus and the cytoplasm is stuffed with either coarse deeply blue or black staining granules. *Endothelial cells* are derived from the

endothelial lining of the blood capillaries and appear as flattened cells with a flattened nucleus showing a well marked nuclear network. The *irritation cell of Turck* is derived from the spleen and is frequently encountered in cases of malarial cachexia. The cell generally takes a faint stain and the nucleus is round and placed eccentrically. The cells are about the size of large lymphocytes. *Lymphoblasts* are characteristic of the blood in lymphoid leukaemia. The cells are larger than the large lymphocytes and both the nucleus and cytoplasm take a poor stain. In the forms with a single nucleus a spherical chromatin staining dot is often seen in the cytoplasm of the cell and would appear to be a centrosome. Forms are also encountered in which the nucleus consists of two separate lobes which touch one another at one point—the *Rieder's cell*.

RED BLOOD CELLS.

Total number	5,000,000 to 6,000,000
Hæmoglobin percentage	80 to 100
Colour index	0.75 to 1.0

Normal variations of number of red cells in a cubic millimeter of blood (Normocythemia).

At birth. Average, 5,500,000. Total range, 5,000,000 to 7,000,000.

From one month to sixteen years. Average, 4,500,000. Total range 4,000,000 to 6,000,000.

Adult males aged nineteen to thirty years. Average 4,800,000 per cent., of men 4,700,000 to 6,100,000 Total range of men 4,200,000 to 6,400,000.

Adult females aged nineteen to thirty years. Average, 4,800,000. 90 per cent. of females 4,300,000 to 5,300,000. Total range of females, 4,070,000 to 5,550,000.

RED CELL COUNT. Capillary blood from the fingers is used as in a white cell count. The blood is sucked into the pipette up to the mark 0.5 and is diluted with Hayem's R.B.C. fluid (mercury bichloride 5 gr., sodium chloride 9 gr., sodium sulphate 46 gr. and distilled water to 4 oz.) and drawn in up to the mark 101. The pipette containing the diluted blood is shaken well. Before placing a drop on the counting chamber, a few drops from the pipette should be discarded as in the white cell count. The same precaution is taken while placing a drop over the ruled lines on the counting chamber. All the cells in 5 large squares (each including 16 small squares) should be counted. To obtain a total red cell count per cubic millimeter add four zeroes to the total cells counted. This is the number of cells per cubic millimeter.

1. *Hypochromia* (Anchromia) is the main change in hæmorrhagic or chlorotic anæmia. Red cells show less colour in the centre.

2. *Poikilocytosis* occurs in any moderate or severe anæmia.

3. *Anisocytosis* is most marked in hyperchromic, macrocytic anæmias of the pernicious type and less so in other hæmolytic anæmias. It does occur in hypochromic microcytic anæmias due to hæmorrhage

but not until the hypochromia is very marked. The Price-Jones diameter curve is a precise method of recording this observation. The halometric method is a valuable substitute.

4. *Nucleated red cells* occur in anæmias where the immature cells are called out. The very severe chronic anæmias like pernicious may call out the very primitive megaloblast.

5. *Basophilic stippling* with a red cell count from 3 to 5 million is suggestive of lead poisoning, although it is not present in all cases.

6. *Polychromatophilia* is found in any severe anæmia.

MEASUREMENT OF THE SIZE OF RED CELLS. The diameters of cells are measured by ruled lines in the eyepiece of the microscope and the results of 200 cells noted. The results when plotted in a chart are typical for normal blood, secondary or pernicious anæmias. It is a quantitative measure of anisocytosis

Halometric reading. Parallel rays of white light passing through a grating of red blood cells on a glass slide are broken up into the colours of a concentric spectrum. The size and character of this circular spectrum or halo indicate the average cell diameter and the degree of irregularity in size and shape of at least 1,000,000 cells. The smaller the particles the larger the halo and *vice versa*. The whole examination requires less than five minutes.

HÆMOGLOBIN. 1. *Estimation by the paper scale (Tallquist)* A small drop of blood from a finger prick is put on a piece of absorbent paper and the paper is folded so as to blot the drop at once. This gives a layer of blood having a uniform thickness. Compare the colour immediately with the scale given in the book, using daylight coming from over the shoulder. Normal 80 to 100 per cent. The margin of error is 10 to 20 per cent. depending on the experience and skill of the examiner. It is not possible to detect any hyper-hæmoglobinemia by the paper scale.

2. *By hæmoglobinomometer of Sahli.* In the Sahli apparatus a standard hæmatin solution is contained in a sealed narrow glass tube. By means of a fine pipette 20 cmm. of blood are drawn up from a drop on the finger tip and immediately transferred to a small, calibrated tube. Into this tube has previously been placed a small quantity (up to the mark 10) of 1/10 hydrochloric acid. The mixture is allowed to stand for a few minutes until the red hæmoglobin of the blood has been changed by the hydrochloric acid into brown acid hæmatin. Distilled water is added drop by drop until the colour in the open tube is exactly that of the sealed standard tube. With normal blood the two tubes become equal in colour at a dilution of about 100 while in hæmoglobin-poor specimens this point is reached at a lower dilution. The percentage of hæmoglobin may be read directly from the scale on the side of the tube. The standard tube of the Sahli apparatus fades upon prolonged exposure to light and should, therefore, be calibrated frequently.

3. *By Hellige apparatus.* An improvement on the Sahli principle is incorporated in the Hellige apparatus. It consists of colour prisms which are accurately standardised with the colour of blood and are absolutely independent of outward influences. The procedure is the same as with the Sahli Hæmometer. After having filtered the graduated tube to mark 10 with 1/10 hydrochloric acid, 20 c.mm. of blood is taken from the patient and transferred to the measuring tube. The blood is mixed thoroughly with the hydrochloric acid. Water is slowly added after about one minute and constantly shaken until the mixture matches the colour of the standard prism.

Colour index is a term used to express the average hæmoglobin content of the corpuscles of a given blood. It is obtained by dividing the percentage of hæmoglobin by the percentage of red cells (5 millions per c.mm. being taken as 100 per cent.). Thus a blood with 60 per cent. of hæmoglobin and a red count of 2.5 millions (=50 per cent.) has a colour index $\frac{60}{50}=1.2$. In secondary anæmia the colour index is considerably below 1, in pernicious anæmia it is about 1 or over owing to the presence in the blood of many large red cells.

FRAGILITY OF THE RED CORPUSCLES. Red cells can remain for hours in isotonic salt solution without damage, but in distilled water they are quickly hæmolyzed. The fragility of red cells is determined as follows: A drop of blood is added to a series of tubes, each containing 1 c.cm. of different strengths of hypotonic salt solution varying from 0.25 to 0.7 per cent. Each tube is shaken and allowed to stand for two hours at room temperature. If no hæmolysis occurs, the unchanged corpuscles are found at the bottom of the tube, overlaid with colourless solution. If hæmolysis takes place, a transparent red solution results. Normally hæmolysis begins at 0.45 per cent. and is complete at 0.35 per cent. In acholuric jaundice the corpuscles are excessively fragile, and hæmolysis may begin with as high as 0.7 per cent. and be complete at 0.45 per cent. In most other anæmias, the resistance is increased, depending on the severity of the anæmia where hæmolysis may not begin until 0.36 per cent. and complete before 0.24 per cent. After splenectomy also the resistance of the red cells increases.

ABNORMAL RED CELLS. The red corpuscles may vary in shape, in size, and in their staining reactions. They may be distorted in shape—*poikilocytosis*; or be unduly small—from 1μ to 6μ when they are termed *microcytes*; or unduly large 10μ to 18μ when they are termed *macrocytes*. Where marked variation in size of the red corpuscles is present, the condition is termed *anisocytosis*. Regarding its staining reactions, *achromia* is characterised by pallor of the central portion of the stained red cell and in the fresh blood by a vacuolation in the centre of the cell. Immature red cells frequently show *polychromatophilia*, the stained cells taking on a brownish to a dirty blue tint.

Granular basophile stippling may be present in the form of blue-staining fine dots on the pink background of the stained cell, and such basophile stippling is found in many severe anæmias, in the leukæmias, in malarial cachexia and above all in lead poisoning. The punctate basophilia may coexist with polychromatophilia in the same cell. A cell which is very characteristic of benign tertian malarial infections is the *demicune red cell*. This cell stains very faintly. The red blood corpuscles having been derived from a nucleated parent cell, remains of the nuclear apparatus may occasionally be encountered within them. These may take the form of small irregular fragments of chromatin, or *Howell's bodies*. Howell's bodies are small spherical masses of chromatin of varying size in the cytoplasm taking on the violet stain of the chromatin. *Chromatin dust* may also be present in a red corpuscle in the form of single or double tiny red granules, usually seen at the periphery of the cell and in size smaller than Howell's bodies. *Cabot's rings* are loops, and figures of eight, or irregular lines—apparently in the membrane of the red corpuscle—which take a red stain. They are especially well seen in Giemsa-stained films from cases of severe anæmia.

Normoblasts or nucleated red corpuscles are of the same diameter as the non-nucleated red corpuscles and have large round intensely stained nuclei, which nearly fills the cells and the cytoplasm of the normoblast stains pink or not infrequently shows polychromatophilic staining. The parent red cell or *megaloblast* and the normoblast appear in the blood films in cases of severe anæmia. The megaloblast has a diameter of 10μ . with a nucleus which is irregular in shape. The nucleus is poorer in chromatin than that of the normoblast, stains less intensely and has a less distinct outline.

BLOOD PLATELETS. These were first detected by Bizzozero in 1882 as the third formed element of the blood. They are essential to life and play an important rôle in the physiology of blood. Wright holds that they arise from the giant cells or megakaryocytes of the bone marrow, which are large cells about 40 microns in diameter. Schilling and Watson believed that these were derived from erythrocytes. Brown thought that hyperplastic endothelial cells in the bone marrow and mononuclear cells in the marrow, spleen and blood could also give rise to platelets. Others hold that these are formed from leukocytes. Functionally the thrombocytes are essential to the coagulation of the blood, contributing some substance necessary to the process of coagulation.

The average diameter of a platelet is from 2 to 4μ (from $1/5$ th to $1/2$ the diameter of a red cell). They stain well with Wright's or Giemsa's stain. Their specific gravity is less than any of the other formed elements of the blood and they are pure white in color. They are minute, labile and agglutinable; chemically they contain nitrogen, phosphorus,

glycogen, and lipoids of phosphatid character. For practical purposes a count varying from 150,000 to 500,000 cells per c. mm. may be considered as normal for adults and older children. The count is however very sensitive and widely varies.

They decrease after injections of benzol, calcium, antimony, tissue extract, tuberculin, corpus-luteum extract, peptone, and bacterial toxins, and also after a diet poor in either vitamin A or B. They are artificially increased after splenectomy, blood transfusion, subcutaneous injection of blood and protein shock, physical work, inhalation of carbon dioxide and monoxide and small doses of X-rays or radium.

They decrease in eclampsia, uræmia, kala-azar, malaria (just before rigors) in anaphylactic shock, in aplastic anæmia, acute lymphocytic leukaemia, purpura hæmorrhagica, Addisonian anæmia, during the incubation period of the infectious diseases, (influenza, influenzal pneumonia, epidemic meningitis, in measles (during the period of the rash). They are increased in chronic active tuberculosis, polycythemia, sometimes in hæmophilia, chlorosis and chronic myelocytic leukaemia, in acute rheumatic fever during the febrile period, in Hodgkin's disease, in secondary anæmia after hæmorrhage, post-operative and post-parturition periods, some types of Banti's disease. In the hæmorrhagic diathesis when the platelets fall below the level of 35,000 per c.mm. spontaneous bleeding into the tissues or oozing from the mucous membranes occurs.

The average life of a blood platelet is 3 or 4 days after which it is destroyed by the splenic macrophages and the sinus endothelium of the reticulum. The spleen also seems to act as an emergency reservoir for the thrombocytes. After splenectomy the reticulo-endothelial system takes over the function of destroying the platelets. Leucocytes are also described to take a part in the phagocytosis of the platelets.

Methods for increasing the platelets in thrombocytopenic states are splenectomy, blood transfusions, injection of foreign protein and other products such as corpus luteum extract, repeated injections of adrenalin, the use of ultra-violet rays, living in a high altitude and injection of calcium salts, atophan, peptone, etc.

A number of methods of platelet count have been devised none of which is absolutely accurate. The direct technique similar to that used for red cell count has many objections. The most reliable technique consists of mixing the blood immediately with citrated or oxalated cresyl-blue solution and then counting the relative numbers of platelets and red cells on a slide under the microscope. From the total red cell count the number of platelets may be estimated.

Reticulocytes. At birth 80 to 50 per cent. of the red cells in the circulation are reticulated but their number drops during the first week to 1 per cent. at which it remains through life. Their number is increased whenever red cells are being rapidly manufactured.

Reticulocyte counting is a means of estimating the rate of red cell production. A small drop of fresh blood is mixed with two big drops

of cresyl-blue solution. A drop of diluted blood is transferred to a clean glass slide and covered with a clear cover slip. The margin of the cover slip is smeared with paraffin. It is then examined under the microscope with an oil immersion lens. The number of reticulocytes among 1,000 red cells is counted and then the percentage is calculated.

SEDIMENTATION TEST. In blood containing an anticoagulant, the cells settle down leaving a clear plasma. This sedimentation is more rapid in disease than in health. A measurement of its rate is of value in diagnosis and prognosis in various pathological conditions. In women during menstruation and gestation, sedimentation takes place rapidly. It is accelerated in most acute febrile diseases and in exudative tuberculosis. In anæmia, diabetes and nephrosis it is accelerated; in jaundice and hepatic diseases retarded. There is no adequate explanation of this phenomenon. This test is performed by taking blood in 3 per cent. sodium citrate solution or by adding 2 to 3 mgm. of potassium oxalate per c.cm. of blood and allowing it to stand in a Cutler tube.

Normal. Men 2 to 10 mm. and women 2 to 15 mm. in one hour when the blood column is 50 mm. high. Changes occurring in the first thirty minutes are of greatest importance.

If a patient complains of illness and no pathological lesion can be found, a rapid sedimentation rate will indicate the existence of some obscure, serious disease. It is of value in prognosis. Recovery is well under way when the sedimentation rate approaches normal.

Diseases influencing the sedimentation rate. Pelvic cellulitis, advanced suppurative appendicitis, mastoiditis, suppurative sinusitis, empyema of gall bladder, pneumonia, endocarditis, infectious fevers, active tuberculosis, syphilis, malignancy in all but early stages, pregnancy (after third month).

(1). **AGGLUTINATION REACTIONS.** After inoculation or infection, substances which agglutinate the specific type of invading organism are found in the blood serum. A standard bacterial culture or antigen if agglutinated by a high dilution of the serum from a patient indicates infection or inoculation by that organism. A standard serum containing agglutinating powers for only one type of organism may be used to identify that organism.

(2). **BLEEDING TIME.** Duke's method. Make a deep prick in the lobe of the ear, and at intervals of 30 seconds, take up the drops as they exude with a piece of filter paper, care being exercised to avoid touching the skin. Note the time elapsed when clotting occurs. Normally the continuance of bleeding is not more than two or three minutes. A prolonged bleeding time indicates capillary wall defect due to toxins or lack of nutrition. The bleeding time is greatly increased in thrombocytopenia and in chloroform and phosphorus poisoning. In hæmophilia the bleeding time is usually ~~not~~ prolonged.

(3). **COAGULATION TIME.** There are two methods:—(1) By Wright's coagulometer. This consists of several fine capillary tubes into

which blood is drawn at definite intervals and at varying intervals they are blown out. When the blood cannot be blown out it has coagulated. Note the time in each case. The difference of the time indicates the actual coagulation time of the sample of blood. (2) By a long fine capillary tube into which the blood is drawn and the time noted. A little part of the tube is broken at intervals until a fine thread-like substance is produced in the broken part (fibrin-thread). The time of appearance of the thread is the coagulation time. The average time is about 3 to 4 minutes. Age and sex do not influence the rate.

Coagulation time is increased in hæmophilia, kala-azar, certain cases of pernicious anæmia, jaundice, splenic anæmia, leukæmias, urticaria, etc.

(4). **COMPATIBILITY TEST.** A sample of the patient's blood is mixed with an equal quantity of sodium citrate and to this is added one-fifth of its volume of similarly treated blood from the donor. The proportion of the respective bloods is the same as that in the patient after a large transfusion. The addition of the citrate makes any clumping more apparent. A transfusion should never be given if the donor's and patient's blood are incompatible by this test. (For details see page 54).

(5). **PEROXIDASE REACTION.** This is done in order to differentiate leucocytes of marrow origin from those of lymphatic origin. The granules in the leucocytes of marrow origin take a deep blue stain. Granules of polymorphonuclears and eosinophiles, myelocytes and myeloblasts are stained intense blue. The large mononuclears and transitionals show few black granules.

(6). **ICTERUS INDEX.** By comparing the colour of the blood serum or plasma with fixed standards a definite figure is given for the degree of bile pigment concentration. (1) Normal 4 to 7. (2) Latent icterus 7 to 18. (3) Bile in the urine and jaundice at 18 or more. (4) Secondary anæmia 2 to 4. (5) Pernicious anæmia 7 to 20. (6) Pneumonia and septic infections 4 to 15. (Above 10 in fatal cases.) (7) Chronic heart failure 4 to 15. (Above 6 in passive congestion of the liver.) (8) Cholelithiasis 4 to 7. (9) Cholecystitis 7 to 15. (10) Occlusion and cholangitis of the common bile duct 30 to 150. (11) Arsenical hepatitis from treatment of syphilis 10 to 150. Gastric ulcer, rheumatic fever, syphilis, tuberculosis 4 to 7. Duodenal ulcer 7 to 14. Diabetes 7 to 15.

Techniques for collecting blood. **Venepuncture.** The median basilic vein at the elbow is one of choice in venepuncture in general practice for collecting blood. Absolute asepsis of the overlying skin is of extreme importance in the procedure. This is generally effected with absolute alcohol, or with tincture of iodine. It is always well to ask the patient to lie down to avoid the risk of fainting, particularly in nervous patients. The vein is made prominent by applying

a tourniquet above the elbow and asking the patient to open and close the hand alternately. Immersion of the arm in a hot water bath might also hasten the process. In fat subjects the vein is generally palpated before introducing the needle. A clean, sterile and dry record syringe is generally used to withdraw blood from the vein. As soon as the blood is withdrawn the needle may be taken off from the nozzle of the syringe and the blood transferred to the tube. This procedure best applies to adult patients but infants' blood is usually withdrawn from the external jugular vein or the longitudinal sinus (anterior fontanelle). Sometimes capillary blood, in infants, is also used for the purpose.

Blood from the external jugular vein. A clean, sterile and dry glass syringe with a needle 1 to 1½ inches in length is generally used. The child should be wrapped up in a small sheet. One person should hold the shoulders and the body and another should fix the head, hanging over the edge of a table and turned to one side. After proper sterilisation of the skin of the neck, the needle is pushed into the vein, which often dilates and becomes prominent as the child cries, at an angle of 20 degrees to the skin surface. There is little danger of damage to the underlying vital structures during such procedure. The blood is then transferred to a tube as before.

Blood from the longitudinal sinus. In infants with fat necks, the longitudinal sinus may be used for withdrawal of blood as the anterior fontanelle remains usually open up to the age of eighteen months. With the same aseptic precautions as were adopted for puncture of the external jugular vein and the head being shaved beforehand and held in position by a nurse, the needle of the syringe is inserted at the posterior angle of the fontanelle making an angle of 20 degrees to the skin surface and not more than 1/8 inch deep. Puncturing brain substance, though not fatal always, should always be avoided.

Collection of capillary blood. The blood is collected from the lobule of the ear or the finger. The part should not be cold, oedematous or congested. With proper aseptic precautions, an incision or a stab wound is generally made with a sterile fine-pointed lancet on the back of the second or the third finger, a little behind the nail bed. The depth of the wound should not exceed more than 2 mm. The finger is grasped well and is flexed. Blood wells up in drops. When the lobule of the ear is used its lower border should be used for incision.

Collection of arterial blood. A puncture is generally made where the artery runs a superficial course. Blood is withdrawn from the brachial, the radial or the femoral artery. The overlying skin is thoroughly sterilised and the part is anaesthetised with a local anaesthetic like 2 per cent. novocaine. The needle of the syringe is inserted at an angle of 45 to 60 degrees directing it towards the arterial pulsation and the syringe fills without suction. No untoward results follow such a procedure. After withdrawal of the needle, the punctured spot should,

in all cases, be evenly pressed with firm pressure for some time, to avoid the formation of a local hæmatoma.

Collection of specimens. No special preparation is usually necessary except that the blood should be drawn in the morning before the patient has any food; it is essential however that the specimen is properly labelled and sent to the laboratory immediately after collection.

The following table gives an idea of the approximate quantity of blood required and the method of collection.

Estimation of or Examination for			Quantity of Blood in c.cm.	To be collected in :
Sugar 2	Oxalated tube.
Urea 2	" "
Non-protein nitrogen 5	" "
Cholesterol 3	" "
Calcium 3	Sterile test tube.
Van den Bergh's test 5	" " "
Aldehyde test 2	" " "
Antimony test 2	" " "
Widal reaction 2	" " "
W. R. 3	Clean phial or test tube.
Culture 5	Broth tube.
Grouping 5	2 c.cm. in citrate tube.
				3 c.cm. in test tube.

PARASITES OF THE BLOOD. 1. *Malarial plasmodia*. Three common species (in man)—(a) *Plasmodium vivax* (tertian parasite). (b) *Plasmodium malarie* (quartan parasite). (c) *Plasmodium falciparum* (æstivo autumnal parasite).

Methods of examination of the blood. The blood may be examined for malarial parasites (a) in wet preparation, (b) in stained smears. For identification of different parasites *vide* text.

Provocative methods for increasing the number of plasmodia in the circulating blood in patients where blood contains small numbers of parasites have been advocated. After a subcutaneous injection of 1 c. cm. of adrenalin, the parasites appear in the peripheral blood in about 20 minutes and the maximum number is obtained in about an hour after such injection. Ergotine, strychnine, application of ice, ultraviolet rays or X-rays over the splenic region have also been advocated.

Ross' thick blood film method and methods for culture of plasmodia *in vitro* (Bass and Johns)—*vide* text.

2. *Filaria*. The embryonal or microfilarial form enters the peripheral blood stream and the examination of such blood is undertaken for diagnostic purposes.

Examination of the blood for microfilaria. A small drop of blood is generally placed on a clean glass slide, the surrounding part is smeared with vaseline to prevent rapid drying and the whole is covered by a clean glass slide.

A better method of detecting the parasites in the blood is to add about 0.5 c. cm. of blood to about 9 c. cm. of 2 per cent. acetic acid. After thorough mixing the preparation is centrifuged and the wet preparation is made from the sediment. The blood for examination should usually be taken at midnight when the peripheral blood exhibits the maximum rise. The embryos exceed by a little the red cells diameter while their length is between 130 and 300 microns.

3. *Trichina*. The embryos of *Trichinella spiralis* may be found in the blood in trichiniasis. At birth an embryo measures 0.1 mm. and grows to about 1 mm. when it becomes encysted in the muscle.

4. *The blood flagellates*. Two groups. (A). *Trypanosoma*. (a) *Trypanosoma gambiense*—African sleeping sickness. (b) *Trypanosoma rhodesiense*—Rhodesian (African) sleeping sickness. (c) *Trypanosoma cruzi*—Chagas' disease.

Trypanosoma. *Trypanosoma gambiense* Length from 15 to 30 microns. As they occur sparsely in the blood a method of concentrating them is necessary.

Method of concentration (Craig). Ten c.cm of blood is mixed with 1 c. cm. of 6 per cent. sodium citrate solution; the citrated blood is centrifuged 3 times; the final deposit contains all the trypanosomes. This is a better method for detecting the parasites than simply wet blood preparations. Auto-agglutination of the red cells should be looked for as this is frequent in infection with *trypanosoma gambiense* and *rhodesiense*. The other type presents similar diagnostic features.

(B). *Leishmania*. (a) *Leishmania donovani*—Kala-azar. (b) *Leishmania tropica*—Oriental sore. (c) *Leishmania braziliensis*—American leishmaniasis.

Leishmania donovani. In blood the L. D. body is seen as a small rounded or oval body, 2 to 4 μ in diameter, within the monocyte or neutrophil. The scarcity of the parasites in the peripheral blood has led to methods for increasing their number. One c.cm. of adrenalin is injected subcutaneously or 0.1 to 0.2 gm. of an organic antimonial intravenously. This produces a splanchnic contraction with the squeezing out of the parasites from the splenic pulp into the peripheral blood. The parasites may also be demonstrated by examination of the material from splenic puncture and culture from the blood.

Leishmania tropica. Successful diagnosis depends on the detection of the parasites by examining material from the lesion of the skin.

5. *Spirochetes of the blood*. Direct examination of the blood is necessary in (a) relapsing fever, (b) infectious jaundice, to detect the particular parasites. There are two methods for staining films for spirochetes; (1) Giemsa's rapid method, (2) Fontana's method.

Relapsing fever (Treponema recurrentis). Length of the parasites 10μ to 20μ . Generally found in the blood during fever. The thick drop method is of advantage when parasites are scanty in the blood. The parasites, unlike *T. pallida*, stain easily with Wright's stain.

Infectious jaundice (Leptospira icterohemorrhagica). Length 5 to 25μ . Direct examination of the blood is necessary to detect the parasites. The parasites are found in numbers in the peripheral blood towards the end of the second week.

BACTERIOLOGICAL EXAMINATION OF BLOOD It is often necessary to make a bacteriological examination of blood and it is a safe and sound rule that when a patient has *continuous fever for three days or more and the cause of such fever is unknown a blood culture should be undertaken*. (In health the blood is sterile and the recovery of organisms from it during life is of pathological significance). Bacteria may be found in patients supposed to be suffering from septicæmia or pyæmia. (1. spread from a septic focus—streptococci, staphylococci, anthrax, 2. general infections—typhoid, plague, meningococcal infections, pneumonia, undulant fever and 3. infective endocarditis).

In the Enteric group of fevers blood culture offers the most definite means of diagnosis but it must be carried out early in the disease (it is also positive in relapse). To do a blood culture properly the following method is recommended.

Apparatus, etc. 1. Sterile syringe and needle (a well-made 10 c.c. syringe with a sharp-pointed moderately stout needle).

2. Culture media. (One or more of the following in flasks containing 50 to 100 c.c.). (a) Peptone-water with $\frac{1}{2}$ per cent. sodium taurocholate. (b) Nutrient broth with $\frac{1}{2}$ per cent. sodium taurocholate. (c) Sterile ox-bile. (d) Sodium taurocholate $\frac{1}{2}$ per cent. in distilled water. (This or even distilled water alone may be used in an emergency where other media are not available. Note that the laked blood serves as a nutrient medium. (e) One per cent. glucose broth (f) When anaerobic cultures are also desired appropriate media (such as minced meat-broth) must be arranged for. Remember this is most important in cases suspected of *Br. abortus* infection or anaerobic streptococcal infections.

3. Tourniquet—a piece of stout rubber tubing, 2 feet long (or a bandage).

4. Sterile swabs, towel and tincture iodine.

The actual technique. Sterilise the syringe with the needle. This is best done by drawing up hot olive oil (heated with a spirit lamp to just boiling, $140^{\circ}\text{C}.$). The syringe can be previously sterilized and carried in a large sterilized test tube plugged with cotton wool and the whole covered. (NOTE:—Boiling at 100°C cannot destroy spores) but if the syringe is kept scrupulously clean, boiling for 15 minutes will suffice. After taking all necessary precautions, 10 c. cm. of blood should be withdrawn. Inoculate the appropriate medium. Remember to protect the mouth of the flask from contamination and to

flame the mouth. Collect the last c. cm. or so of blood in a sterile tube for agglutination test.

Incubate at 37°C. for 24 hours and examine flask for growth. If there is evidence of growth in the enrichment broth, inoculate media in plates from the flask, using one plate of MacConkey's neutral-red-lactose-bile salt-agar and a plate of blood agar. If after twenty-four hours incubation these plates show no growth of bacteria incubate them further for forty-eight hours more. In case no growth appears but there is evidence of growth in the broth culture, plate the broth again, keep the original flask for two weeks as growth is sometimes delayed and even if no visible growth be seen in the broth it is advisable to make and examine films and to subculture at intervals of 48 to 72 hours on to solid media. It is advisable not to open the flask too often in order to avoid any risk of contamination. Blood clots from specimens submitted for agglutination test can be utilized for cultural examination if necessary. Do not plate such specimens directly, but break up the clot with sterile forceps and transfer it to a bottle containing some medium (Glucose broth). Then proceed as above. When it is necessary to perform blood culture at a distance from a laboratory and to transmit the specimen by post, the most convenient method is to forward the bile in sterile 25 c. cm. vaccine bottles provided with rubber caps. The blood can be introduced directly through the rubber cap into the bile. The needle puncture sealed and the whole wrapped and sent to the laboratory.

BLOOD PRESSURE. By blood pressure is meant the pressure that the blood exerts against the wall of the vessel in which it is contained. The term, therefore, includes endocardial pressure, arterial pressure, venous pressure and capillary pressure. But clinically, blood pressure usually refers to the tension of the arteries only and depends on the following factors :—(a) The force of contraction of the left ventricle. (b) The volume of blood which the left ventricle propels into the already full arteries. (c) The elasticity of the middle coat of the large arteries. (d) Lastly, the peripheral resistance or the resistance to the outflow offered by the arterioles. These factors are under the control of the vagus and the vasomotor centres and the brain can adjust the blood pressure to suit its needs. The carotid sinus appears to be the most important centre for the control of blood pressure. The activities of the vagus and the vasomotor centres are regulated by reflexes from the carotid sinus. Any rise of pressure in the sinus causes slowing of the heart and dilatation of the arterioles whilst a fall of pressure produces the opposite change. The arterial pressure of the body at rest may be said to be the lowest pressure at which the brain can obtain an adequate blood flow. The blood supply to different organs and tissues of the body depends on the efficient working of the heart and the maintenance of a certain amount of tone in the arterioles supplying blood

to them. The arterioles are richly supplied with vaso-constrictor nerves and always maintain a certain amount of tone, which is constantly regulated by the vasomotor centre in the medulla through the vaso-constrictor nerves. When there is a general rise of pressure, the action of the vasomotor centre is re-inforced by the suprarenal glands which produce an increased output of adrenalin thus causing a further constriction of the vessels and adding to the already existing increased blood pressure. The arteries and arterioles are relatively thick-walled vessels and the blood in them is under considerable pressure and moves with a fair velocity. The blood in the aorta is at a pressure of about 120 mm. Hg. and moves with a velocity between 100 and 200 mm. per second during systole. The velocity and the pressure decrease as the vessels branch and become smaller but both remain considerable as far as the arterioles. The arterioles open into the capillaries where the pressure is only 10 mm. Hg. and the velocity of the blood is about 1 mm. per second.

Essential hypertension may be described as a persistently raised systolic and diastolic blood pressure not due to arterio-capillary, renal, cerebral or other recognizable morbid change. It may, however, cause and be the antecedent stage of cardiovascular changes, renal fibrosis and other pathological conditions. It has often been suggested that high blood pressure is a compensatory adaptation to maintain an efficient circulation through the kidneys, brain and myocardium. Starling suggested arteriolar proliferation in the vasomotor centre as the cause of hypertension. MacWilliam concludes that the hypertensive impulse however caused, emanates from the controlling vasomotor centre in the medulla. Vasomotor instability is present in many cases of hypertension. It is conceivable that a metabolic poison selectively constricts the arterioles of the vasomotor centre and the resulting ischaemia stimulates pressor impulses. Clinical observation shows that arteriosclerosis and high blood pressure, though often associated, occur independently and that long-continued hypertension is more responsible for degenerative arterial changes than *vice versa*. Volhard and Fahr have made a division between benign and malignant hypertension. The malignant form is complicated with diffuse changes in the arterioles. It mainly occurs about the fourth decade and runs a rapid course with very high blood pressure. Death may result from apoplexy or acute functional failure of the brain, myocardium or kidneys. Malignant hypertension thus differs from uncomplicated essential hypertension. Hoyle (1933) showed a pressor substance in the urine of hypertensive subjects (during adolescence) with a physiological action upon the cardio-vascular system similar to that of adrenalin and allied pressor bases. Clifford Allbutt (1895) held that persistent high arterial blood pressure is not secondary to chronic kidney disease and suggested as an alternative the word 'hyperpiesis' and pointed out that persistent high arterial pressure was not confined to the elderly only. He eventually restricted the use of the word 'hyperpiesis' to the high sphygmomanometric reading and employed

the modified title 'hyperpiesia' for the clinical condition. The essential pathological change consists in a hypertrophy of the middle or muscular coat of the arterial wall affecting principally the medium and small sized arteries of the body. Broadbent (1890) applied the term 'virtual tension' to the impression conveyed to the finger by arteries worn out and dilated by old-standing high blood pressure when the heart is failing. Huchard (1893) wrote on 'hypertension' and introduced the word 'presclerosis.' The term 'essential hypertension' is rather confusing and so O'Hare in advocating the heading 'vascular hypertension' points out that it is better to use a simpler term than one, the meaning of which is not at once obvious, though Sir Thomas Lewis in his recent and concise account adopts the title 'essential hypertension.' Rolleston holds that the word 'essential', though probably better than 'idiopathic' is not so good as 'primary.'

ÆTIOLOGY *Predisposing factors.* Heredity has been rightly considered to be a predisposing factor. Weitz concludes that 'genuine or vascular' hypertension is a constitutional disease with dominant Mendelian characters. Males suffer more than females due to stress and strain of life. *Exciting causes.* These are sedentary habits and factors leading to intestinal toxæmia; toxic blood states, renal disease; metabolic diseases like gout and diabetes; psychical causes such as worry, anxiety and prolonged mental strain; plethora; cardiac hypertrophy; neuro-vascular diseases like Raynaud's disease and certain endocrine disorders such as excessive secretion of adrenalin or vasopressin. It has been suggested that hypertension is due to overactivity of the chromaffin system and hyperplasia of the adrenal medulla, though adrenalin has not been found in excess in the blood of hypertensive subjects. MacWilliam holds that deficiency of hypotensive bodies in the circulation is a possible cause of hypertension.

Clinically there may be no symptoms and the discovery of high blood pressure may be purely accidental. Subjective symptoms experienced by the hypertensive subject may be headache, cardiac symptoms such as præcordial pain and palpitations, nocturnal frequency of urine, dizziness, nervousness, fatigue, symptoms of cerebral vascular lesions, ocular symptoms, epistaxis and hæmoptysis.

Methods for determining blood pressure. William Russell (1921) states that the finger is still the main means of estimating blood pressure in clinical work. This view is based on the belief that considerable pressure may be required to obliterate an artery thickened by degenerative changes, or in a state of hypertonus. It is usually thought that the force thus expended in blood pressure determinations is comparatively negligible, but Russell, from experimental observations concludes, that in some instances a pressure of 150 mm. Hg. or more may be required to compress a thick artery.

It is quite impossible to determine, even approximately, the diastolic pressure without instrumental aid. It is important to investigate

it for several reasons. The diastolic pressure may be raised without corresponding increase in the systolic pressure. This involves a continuous increased strain on the vessels. The prognosis with a constant diastolic pressure of 135 mm. Hg. or over is very grave. The diastolic pressure may be abnormally low, although the systolic is raised, this is found typically in aortic regurgitation with a free reflux. It is necessary to determine the diastolic pressure in order to calculate the pulse pressure. An increased pulse pressure is associated with hyperthyroidism. Another example of the value of instruments in taking blood pressure is the fact that the condition of *pulsus alternans* may sometimes be diagnosed by this means, although it is not perceptible to the finger alone.

The chief methods employed for determining the blood pressure may be classified as follows:—Palpatory, vibratory, oscillatory and auscultatory.

Palpatory. Systolic pressure. Von Basch of Vienna in 1876, first devised a clinical method for estimating the systolic blood pressure in man. He employed a pelote consisting of a small glass funnel connected by a rubber tube with a mercury manometer, the open end of the funnel being closed by an elastic membrane. The pelote and tubing were filled with water. The systolic pressure was determined by compressing an artery, such as the radial or temporal, between the pelote and the underlying bone and at the same time feeling the pulse beyond the site of the pressure. The force required to obliterate the pulse could then be calculated by means of the manometer. Potain (1889) modified this instrument, using a rubber pelote communicating by air transmission with a metal manometer. Reading by either of these forms of sphygmomanometers gives figures for the systolic pressure, which are often 50 to 60 mm. (Hg.) higher than the normal.

Riva-Rocci (1890) introduced the method of compressing the artery by means of an armlet encircling the limb, into which air is pumped. His instrument is well known and constitutes the most accurate means of estimating clinically the systolic blood pressure in man. The results obtained are about 7.5 per cent. higher than the true systolic pressure. Care must be taken to determine the residual systolic pressure by making several estimations until a constant reading is obtained. The point at which the pulse disappears on compression should be determined rather than its point of reappearance on decompression. The mean of these two readings is often taken as the systolic pressure.

Diastolic pressure. Strasburger (1904) described a method for determining the diastolic pressure with the Riva-Rocci apparatus. The radial pulse is carefully felt while the armlet is slowly inflated, and a point is noticed at which there first occurs a diminution in the force of the beat. This indicates approximately the diastolic pressure, but the figure obtained is a little high. *Vibratory method.* This is a method for determining the diastolic pressure only. When the pressure is

slowly raised, as in Strasburger's method, just before the pulse becomes perceptibly smaller, the artery suddenly pulsates vigorously, giving a strongly vibrating sensation. This is much more clearly appreciated if the brachial rather than the radial artery be palpated. As the pressure is further raised these forcible vibrations first increase and then decrease in intensity (variations of 5 mm. on the pressure scale), and are then replaced by normal beats which disappear when the systolic pressure is reached. On lowering the pressure the reverse takes place, and the point at which the vibrations disappear on decompression is usually 2 to 3 mm. lower than that at which they are first noted on compression and these are well marked in cases of high blood pressure. The diastolic point is taken as that pressure at which the first normal beat follows a vibrating beat on decompression.

Oscillatory. This is a method for determining both the systolic and diastolic blood pressures. It is found with the aid of Pachon's oscillogram and Erlanger's sphygmomanometer. The former apparatus consists of a rigid metal box, containing a manometric capsule, a pressure manometer and an armlet. The manometric capsule enables the extent of the oscillations to be read at different pressures. It is put into communication with the circuit, consisting of the box, manometer and armlet by means of a screw, and the oscillations read, as the pressure is lowered. Small oscillations are first seen on decompression, which become larger and then decrease in size. The difficulty in interpreting the readings lies essentially in the fact that often there are oscillations at pressures above the systolic figure and below the diastolic. These are called supramaximal and inframinimal oscillations.

The systolic pressure is that pressure at which the first large oscillation occurs on decompression. If there be no supramaximal oscillations present, this is easy to determine; if, however, they occur, the systolic pressure is that point at which the supramaximal oscillations are replaced by larger oscillations. The supramaximal oscillations are due to waves of blood beating against the obstruction caused in the brachial artery by the pressure of the armlet.

Pachon originally said that the point at which the oscillations are greatest was the diastolic pressure. It is however now taken as that point at which the large oscillations undergo a sudden and marked diminution in their size, and become inframinimal. The average diastolic pressure for an adult with the Pachon instrument is about 90 mm. Hg.

Erlanger Apparatus. The oscillations are recorded graphically on a blackened paper travelling with a moving drum. The systolic and diastolic points are as in the Pachon readings, and present the same difficulties of interpretation.

The auscultatory method of Korotkoff is the most practical and widely used. The patient should be comfortably seated with his arm bared to the shoulder and resting on a support so that the muscles

of the arm and the forearms are relaxed. The armlet is applied about an inch above the fold of the elbow. The cuff is inflated by small but rapid compressions of the bulb until the radial pulse becomes imperceptible. The stethoscope is placed over the artery just below the compression cuff, which is then deflated evenly. Five phases in the readings are recognised. The first phase consists of clear-cut snapping sounds. The change to loud rough stenotic sounds is the second phase, which shows partial and at times complete disappearance. Then there is return of the sound similar to phase one, but not so loud, and this is the third phase. The fourth phase is an abrupt dulling of the sound or a change from sharp pistol-shot to dull toneless sound. The disappearance of the sound is the fifth phase. The beginning of the first phase is the systolic pressure and is usually 4 to 6 mm. higher than that estimated by palpation. The true diastolic pressure is the beginning of the fourth phase. In cases of marked aortic regurgitation or vasodilatation the fifth phase may be attended by a dull sound down to zero, then the diastolic pressure must be estimated at the beginning of the fourth phase.

A frequent source of error in cases with raised blood pressure is the 'silent gap' which occurs usually in the second phase. This zone of silence may be absolute or relative, but generally begins 10 to 30 mm. above the diastolic level. It can be produced to a variable degree by obstruction to the peripheral circulation, for example, through venous compression. Its mechanism is unknown, but it is sometimes associated with the shape of the pulse wave, as in the anacrotic or plateau pulse of aortic stenosis.

If several trials are made without completely deflating and waiting for about thirty seconds between readings, there will be venous engorgement with changes in blood pressure, which causes difficulty to identify the phases. A tight roll of clothing at the shoulder may make it impossible to estimate the diastolic level, by causing obstruction sufficient to produce sounds which can be heard to zero and so simulating aortic regurgitation.

The normal pressure varies at different ages, and it may be taken that the average systolic reading for an adult is 100, plus half the age in years, and that in any case a systolic pressure above 150 mm. of Hg. is abnormal. The diastolic pressure is approximately two-thirds that of the systolic up to middle age, but later it may be only half the systolic. A diastolic pressure which is higher than 120 mm. Hg. is of serious significance. In healthy individuals a blood pressure below the average from the standpoint of longevity is an asset. Sir Thomas Lewis says: "The average blood pressure rises with age; this is not to say that rising blood pressure is normal, for many vigorous and long-lived men retain low blood pressure; it is good that an otherwise healthy but aged man should show a pressure below the average for his years." Consequently, there is justification in regarding a blood pressure below

average as the normal. If individuals can perform their daily work with a blood pressure below average they are fortunate as there is less wear and tear upon their tissues, especially their blood vessels and the heart.

The following may be regarded as the normal standard of systolic blood pressure as measured in the brachial artery, while at rest. In children under 10, 100 mm.; in early manhood from 100 to 120 mm.; in middle age from 125 to 135 mm.; above 60 years of age 145 to 150 mm. In the female, the systolic pressure is generally 10 to 20 mm. lower than in the male. The range of diastolic blood pressure, as estimated by the auscultatory method in healthy young adults, is usually accepted as 70 to 90 mm.

There are variations in the blood pressure under physiological conditions, among these being mental states, sensory stimulation, sleep, change of posture, meals and physical exertion. Those of nervous and anxious temperament, as well as those whose mode of life necessitates considerable nervous strain, have a tendency to exhibit higher readings, especially in the later period of life; while in those of an equable and placid temperament, and those whose mode of life is smooth, the opposite is the case. Sensory stimulation often causes a rise in the arterial pressure, especially in the diastolic. In sleep there is a fall of blood pressure. Opinions vary as to the effects of the digestion. It is probable that the change in pressure commences within a quarter of an hour after a meal, the highest reading being reached in about an hour, after which it gradually returns to the normal. During exercise the pressure as well as the pulse rate are raised, returning to normal in half an hour.

The systolic blood pressure shows the greatest variations. It is, usually affected first. Persistent readings of more than 10 mm. above the average are not normal. When hypertension has existed for some time there is enlargement of the heart. The diastolic blood pressure is more stable, and small variations are significant. It is however more difficult to estimate. When over 90 mm. it is suspicious; over 95 it is abnormal; 100 and over is definitely pathological; 110 and over usually means progressive kidney disease or malignant hypertension (Keith). If diastolic pressure is high it means excessive constant strain on the circulation, and if it is abnormally low, it means a serious handicap, because of poor myocardial nutrition. Pulse pressure is a composite of both the systolic and the diastolic. A dropping pulse pressure usually means myocardial failure. Pressure variations from beat to beat may occur with premature beats and in auricular fibrillation. When during normal rhythm, regular variation occurs in alternate beats, one can diagnose *pulsus alternans*. This is one of the most important signs of cardio-vascular failure and is indicated by the sphygmomanometer.

Blood pressure, both high and low, appears to be a familial trait, and has been regarded by some as associated with special constitutions. The characteristic of low blood pressure subjects is a long narrow chest; they are easily affected by cold, easily tired, and of hyposthenic habits. The high blood pressure subjects are broad-shouldered, broad-chested, athletic and are of hypersthenic habits. Constitutional low blood pressure shows no tendency to become progressively lower, but so-called constitutional high blood pressure is liable to become permanently higher.

Hypertension may be divided clinically into three groups according to the order of appearance and seriousness. (I) Both systolic and diastolic pressures are raised with a pulse pressure above normal. Here we have pathological changes in the vascular system, especially the arterics. (II) The diastolic pressure is normal or nearly so, but the systolic is raised and the pulse pressure correspondingly high. This is the so-called stage of 'essential hypertension' or hyperpiesia. (III) The diastolic pressure is high, but the systolic is dropping, giving a low pulse pressure. This is the stage of myocardial failure and may be present for some time without symptoms.

TREATMENT. As normal blood pressure has a wide range of variation in different subjects, before adopting a line of treatment for an individual, inquiries should be made of his previous usual blood pressure, abnormal symptoms if any, the treatment adopted before and the effects following such treatment. The patient should be encouraged to think that a high blood pressure is not so serious if his life is governed by moderation. It is more important to treat the underlying conditions, responsible for the high blood pressure than the pressure itself, when this can be done. A review of the conditions of life is necessary in such a case. Foci of chronic sepsis which may be associated with the teeth, tonsils, nasal sinuses, gall bladder, prostate, etc., should be searched for and eradicated, where possible. Rest should come foremost in the general care of a hypertensive subject. It should be enjoined both mentally and physically. As psychical factors are more important than others in hypertension, absolute mental rest should be aimed at. Halls Dally (1891) advocated the creation of a congenial psychical atmosphere and the cultivation by the patient of an equable, cheerful and balanced temperament. Occupations of steady routine are to be preferred to those that involve constant anxiety and sudden fluctuations. Light reading and similar distractions are useful in getting rid of worries before retiring to rest. He suggests that not less than eight hours be spent in bed, and rest should be enjoined after meals if possible. Holidays should be spent in pleasant surroundings which will give mental relaxation. Sudden exertion, hurry, worry, and straining at stool should always be avoided. When symptoms of hypertension develop, physical rest in bed is imperative and the pressure consequently falls. Myocardial failure also demands absolute rest.

Diet therapy. Diet should be simple, wholesome and small in amount. A tendency to obesity should be controlled and carbohydrate should be restricted if such a tendency exists. Excess of carbohydrates and fats causes flatulent dyspepsia which in turn increases the blood pressure. A high protein diet should never be encouraged as the products arising out of putrefaction of proteins in the intestine are potent causal factors in hypertension. On the other hand, a low protein diet induces anaemia and asthenia and, therefore, moderation in the protein intake should be aimed at. Fresh fruits, vegetables, cereals and fish may form part of the dietary. Eggs, milk and similar products rich in cholesterol should be cut down to the minimum. Drinks like alcohol, tea and coffee should never be freely indulged in. A moderate indulgence in tobacco is probably not harmful while its soothing effects may even be beneficial. Excessive smoking should be forbidden. Ingestion of excessive quantities of fluids is distinctly harmful in hypertensive subjects and it is suggested that one pint of fluid for every five stone of body weight, taken in during the twenty-four hours should be the usual rule. Opinions vary regarding the intake of chlorides. Patients with high blood pressure but presenting no symptoms may be allowed common salt as ordinarily used in the preparation of food, but a strict salt-free diet is desirable in cases where symptoms like palpitation, dyspnoea and oedema have supervened.

Physiotherapy. Exercises, preferably in the open air and only in moderation, may be allowed to hypertensive subjects provided no symptoms of cardiac decompensation appear. Deep breathing exercises, passive movements, general massage are all useful therapeutic adjuncts in lowering high arterial pressure. As regards baths, the value of hot baths is doubtful and cold baths are harmful because they raise the blood pressure; tepid baths (94° to 98°F.) are beneficial. A yearly visit to a spa may be a valuable aid to ordinary treatment. Humphris (1925) refers to the lowering of blood pressure in hyperpiesia by daily application of d'Arsonval electric current. The effect is due to stimulation of metabolism and production of local vasodilatation. High frequency currents lower the pressure for a time. Ultra-violet rays are also stated to have a similar effect. Cyriax (1917) reported good results in cases of moderately high blood pressure, obtained by what he described as 'mobilization of the spinal column' by which he meant active and passive movements of the vertebral joints and passive manipulations, vibrations, petrissage of the erector spinæ muscle. He thought that congestion of these parts led to irritative states of the erector spinæ setting up a series of sensory stimuli to the posterior spinal nerves which in turn gave rise to a series of pressor effects thus raising the blood pressure. Results of treatment were encouraging. Gunewardene modified this method by substituting electrical stimulation of the skeletal muscles.

Drug therapy. Drugs, though of secondary importance, have their place in treatment, more especially in the earlier stages. Later, they are needed to relieve distressing symptoms of cardiac, cerebral and renal origin. No specific drug is known to cure the disease or to alleviate symptoms permanently. A large number of synthetic drugs have been tried but not one is known to have any specific effect in the disease. Treatment with drugs is therefore only symptomatic and emergent and this should go hand in hand with diet and physiotherapy. As constipation and intestinal toxæmia play an important ætiological role in hypertension, purgatives occupy the foremost position in treatment. The daily use of purgatives is obnoxious and it should be noted that slight laxative action of the bowels daily is of greater use than the use of an occasional purge. It is suggested that abdominal massage and bulky carbohydrate foods might help in complete and regular evacuation of the bowels, but this does not suit fat persons who are usually the victims of the condition and are often subjects of flatulent dyspepsia. Carbohydrates increase blood pressure and sometimes give rise to colic and mucous colitis. For regular use, liquid paraffin (1 to 2 oz.) and allied preparations such as petrolagar alone or combined with cascara, serve the purpose best. They all efficiently lubricate the bowels and facilitate the passage of stools. According to some, blue pill overnight followed by a smart saline purge in the morning should be the routine practice of the hypertensive subject at weekly intervals or when subjective symptoms appear. In some individuals a daily dose of saline sufficient to give one or two loose stools keeps the blood pressure down. When actual symptoms of hypertension such as fullness in the head, headache, palpitation, etc., develop, time should not be lost in procuring and maintaining adequate rest and administering depletive remedies such as cholagogue purgatives and the hydragogue cathartics to the patient. Besides the purgatives discussed, a mineral water, where available, such as Hunyadi Janos Friedrichshall, Kissingen, Rubinat or a laxative lithia, along with diet therapy often helps an efficient daily bowel action. In toxæmia resulting from intestinal stasis, rectal injections, every morning for three weeks, of a pint of solution of potassium permanganate (1 gr. to 1 pint of water) is often of great value. Along with such treatment, a simple diuretic mixture with bromides and valerian when the patient is nervous by disposition, is often of much benefit. Sedative drugs are of much benefit in these cases and bromides, chloral hydrate and barbiturates are often prescribed with advantage. One to three tablets of theominal, a combination of theobromine ($4\frac{1}{2}$ gr.) and luminal ($\frac{1}{2}$ gr.) are often beneficial in cases where restlessness is a predominant symptom. Preparations containing valerian are often combined with bromides in neurasthenic cases. For hypertension of menopause in elderly women, bromides with calcium therapy and a polyglandular extract or an extract of ovary, appear to be distinctly valuable. In nervous, excitable and emo-

tional subjects, the use of quinine hydrobromide (3 gr.) or if there be idiosyncrasy the use of ammonium bromide (5 to 10 gr.) has been advocated. Iodides are thought to lower blood pressure by diminishing the viscosity of the blood and also in very minute doses they act as vasodilators. Opinions vary as to the efficacy of iodine preparations in the treatment of hypertension. Potassium iodide in increasing doses has been found of much benefit in persons who have passed middle life; others prefer colloidal iodine, French Codex iodine (5 min. in milk) or a hypodermic injection of an iodine compound such as 'tiodine'. The vasodilators and the hypotensive drugs play an important role in the treatment of hypertension. They are most needed in cases of emergency and though the effects are transient, the use of such drugs is universal. They relieve the heart and blood vessels of excessive stresses, administer rest to the myocardium and are powerful palliatives. These drugs should however be cautiously prescribed as their indiscriminate use might precipitate an apoplectic seizure sometimes. Of the hypotensive drugs, nitrites, mistletoe, preparations of sulphocyanic acid, choline derivatives, veratrum and extracts of certain organs and muscles, deserve special mention. Nitrites are of particular value in relieving symptoms of headache, dizziness and anginal pains. The effects are transient and are of little value in long-standing cases of hypertension. Benzyl benzoate has also been extensively used but this is of disputed value. Good results have been obtained from long-continued use of bismuth subnitrate in the pre-tensive stage of the disease. It is decomposed in the bowel producing nitrate ions which are in their turn, converted into nitrous acid by *Bact. coli* and this maintains continued vaso-relaxation. It is given three times a day in capsules containing 10 gr. of the drug, for several months. Mistletoe is extensively prescribed by French physicians; it contains an alkaloid, a saponin, magnesium and potassium salts and is described as guipsine pills. It has a central action and is not a cardiac depressant; the dose is two pills three times a day. Sodium sulphocyanate is of particular value where organic changes in the arteries are absent. It is prescribed in 1½ gr. doses, three times daily after meals for the first week, twice daily for the second week and once daily for the third week. The drug should be discontinued if a rash appears and it should never be prescribed if the renal functions are impaired. (Elixir sodium sulphocyanate contains sodium sulphocyanate 20 gr. to an ounce.) The choline derivatives act as a specific stimulant of the parasympathetic system and antagonise the action of adrenals. A few of its derivatives are efficient vasodilators of which pacyl (choline content 1½ gr.), acetyl choline and hypotan, deserve a mention. Pacyl and hypotan (methyl acetyl choline bromide) tablets are sold for oral use. The dose of each is 3 to 6 tablets daily. Acetyl choline has a more prolonged action than pacyl or hypotan. It is given as a subcutaneous or an intramuscular

injection and should never be given intravenously. The initial dose is 0.05 gm. increased subsequently to 0.1 gm. daily. The fall of blood pressure is marked and is maintained for some hours. The preparations of *veratrum viride* used in the treatment of hypertension are the tincture of *veratrum* (B. P. 1 dose 5 to 15 min.) and *veratrone*, a synthetic preparation of P. D. & Co. *Veratrone* is injected intramuscularly in doses of $\frac{1}{2}$ c.cm. The drug is of proved value but should be used with caution, as it sometimes produces an alarming fall in blood pressure. Venesection is an efficient hypotensive measure and is particularly useful in congestive cardiac failure in hypertensive cases.

Opothrapy. The extracts of many organs and tissues such as histamine, choline, acetyl choline, adenosine and extracts of liver and brain and internal secretions of the endocrines exert a depressor effect on high blood pressure. *Hepatic extracts.* Anabolin is a hepatic extract and acts by virtue of its histamine content. It is used as daily intramuscular injections, in doses of $\frac{1}{2}$ to 1 c.cm. till the pressure is lowered. Heparhone (Lily) is claimed to be a better drug than anabolin. It is used in the form of intramuscular injection in doses of 2 to 3 c.cm. and is of particular value in early cases without much arterial or renal damage. *Thyroid extract* is useful in obese menopausal patients. It is given in $\frac{1}{2}$ gr. doses, thrice daily. *Padutin*, a hormone from the pancreas is a useful vasodilator in hyperpiesia. It is used as an intramuscular injection in one unit dose, twice daily for three days and later, in two unit doses for nearly a fortnight. It is also prescribed for oral use in doses of 10 drops, three times a day. Recently, another hormone has been isolated from the pancreas and named *vagotonine*. It is a stimulant of the parasympathetic system and exerts a more depressor effect than other tissue extracts and other hypotensive bodies, as *kallikrein*, another hormone extracted from the pancreas. *Lacarnol*, a nucleoside muscle extract, is an efficient preparation for dilating the coronary arteries and the drug is of proved value in anginal attacks. It is used both as intramuscular injections in doses of 1 c.cm., and orally in doses of 10 to 15 drops, three times a day for many weeks. Opothrapy has no doubt relieved distressing symptoms of hypertension but its value as a cure is open to debate.

A few words are necessary on the treatment of low blood pressure. The common ætiological factors responsible for hypotension include acute cardiac diseases, chronic valvular diseases of the heart, especially the mitral, chronic interstitial myocarditis, myocardial degeneration, endocrine dysfunctions, particularly Addison's disease and early stages of Grave's disease, chronic wasting maladies such as tuberculosis, infectious diseases such as enteric fevers, diphtheria, pneumonia; auto-intoxication from septic tonsils, teeth, colon, genito-urinary tract, etc. Considerable loss of fluid from the body results in marked low blood pressure in cases of cholera, acute diarrhoea, dysentery, vomiting, and severe hæmorrhage. The condition is brought about by a diminution of

ventricular output, lowering of the vasomotor tone due to derangement of the vasomotor centre and splanchnic stasis. The cases frequently show symptoms of asthenia, myasthenia, giddiness, faintness, mental depression, nervous instability, sensitiveness to cold, etc. The treatment of hypotension is essentially a treatment of the primary cause. Eradication of the septic foci in the body when detected is most important. Diet should be a mixed one and may be rich in protein content. Meat extracts, meat soups, eggs and milk should be supplied to the dietary in sufficient quantities. Fluid intake should always be encouraged. In cases where loss of body fluid is marked, to make good the loss sufficient fluid should be supplied to compensate the condition. Massage is held by some to be useful in some cases. Wearing of an abdominal belt is a helpful measure in cases of splanchnic stasis. A few drugs are of reputed value in raising blood pressure in hypotension, of which, adrenalin, ephedrine, pituitary extract and strychnine deserve mention. Strychnine and calcium are very much favoured as drugs of efficacy in acute infectious fevers such as diphtheria, pneumonia, etc., where low blood pressure is frequently marked. Saline infusions, injections of adrenalin, pituitary extract or ephedrine are invaluable in raising the blood pressure in cases of haemorrhage, acute diarrhoea, cholera, etc. In cardiac diseases digitalis and strophanthus are of proved value. A change of climate and tonics such as iron, arsenic and glycerophosphates, are most beneficial in the treatment of prolonged convalescence after acute diseases where the blood pressure is generally low.

BOILS. See page 1161.

BRONCHITIS. The inflammation of the bronchi is a most common malady induced by various agents bacterial, chemical and mechanical. It may be acute or chronic affecting both the larger and the smaller tubes. The acute and chronic types are further classified into catarrhal, suppurative and fibrinous or they may be secondary to other causes. Of the predisposing causes climate and latitude play an important role in the causation of the disease. Besides, a hereditary predisposition, extremes of age, fatigue and privation, deformities of the chest, chronic cardiac and renal diseases and conditions of the respiratory passages deserve mention. The catarrh-producing organisms responsible for the condition are pneumococcus, Friedlander's penumo-bacillus, streptococci, *Micrococcus catarrhalis*, staphylococci, *Micrococcus tetragenus* and sometimes *Bacillus coli communis*. *Spirochæta bronchialis* has also been isolated from the sputa of these cases. In suppurative bronchitis Pfeiffer's bacillus influenzae are found in 90 per cent. of the cases. Secondary bronchitis follows diseases like measles, whooping cough, influenza, fevers of the enteric group, small pox, diphtheria and plague. Other conditions associated with bronchitis are pulmonary tuberculosis, secondary syphilis,

pleurisy and penetrating injuries of the chest. The cause of fibrinous bronchitis is not yet known.

Ordinarily three stages are recognised during the course of the disease and these are, an initial dry stage, the second or mucoid stage and the stage of resolution.

An acute attack is usually characterised by malaise, aching of the limbs, a sense of oppression about the chest, a moderate rise of temperature varying from 99° to 103°F., hurried respirations, a flushed appearance of the patient. The cough is at first dry and hacking and the sputum is scanty and tenacious, later with the onset of expectoration it becomes copious and mucoid in character. The temperature usually abates in a week's time. The physical signs as revealed by auscultation of the lungs include sonorous or sibilant rhonchi in the early stages and bubbling rales later on.

Complications of bronchitis are many, of these broncho-pneumonia, lobar pneumonia, bronchiectasis, chronic bronchitis and even active tuberculosis deserve mention.

TREATMENT. The aim of treatment of a case of acute bronchitis should be to maintain the strength of the patient and especially the strength of his heart, to deplete the tubes and relieve cough by promoting free expectoration.

In all cases of acute bronchitis, the patient should be confined to bed and in cold weather the temperature of the room should be maintained at 65°F. During the febrile stage the diet should be summed up in the words 'hot slops' such as milk, weak tea, gruels, broths and other invalid foods as hot liquids tend to promote bronchial secretion. The air of the room may be moistened by means of a steam kettle in the dry stage only. Medicated inhalations are useful and vapour of compound tincture of benzoin (1 dr. to a pint) is very comforting to the patient in the early stage and later on, a dry inhalation of creosote, terebene and spirit of chloroform is considered to be helpful. Of the drugs, in the early stages, a simple saline diaphoretic mixture with the addition of small doses of tincture of ipecacuanha or wine of antimony may be useful. With the onset of expectoration, stimulating expectorants such as chloride and carbonate of ammonia combined with squill and syrups of tolu and virginian prune, are helpful. In the early stages, Dover's powder is highly recommended. When very distressing cough is present compound tincture of camphor may be advantageously added to the mixture. To reduce cough at night or a dry cough, Samuel Gee's linctus is the best for mild cases. This consists of equal parts of compound tincture of camphor, syrup of tolu and honey of squill. The usual dose is a drachm. Resort may sometimes be made to the use of codeine or heroin. Cardiac stimulants should be administered where necessary.

In subacute cases, an autogenous vaccine, when streptococci predominate, is of greatest value, the dose should be small starting with $\frac{1}{2}$ to $\frac{1}{4}$ of a million.

In chronic bronchitis preventive measures should involve residence in a warm dry climate, the patient's bedroom must be comfortably warm. He should not go out of doors in inclement weather. In fat subjects with bronchitis carbohydrates should be restricted so as to bring down the weight of the patient. In-take of alcohol and smoking should be always forbidden. Stimulating expectorants are the most suitable drugs.

During convalescence, a change of climate, nutritious food and a mixture containing strychnine, iron, glycerophosphate, etc., go a long way to speed up recovery and restore the tone of the patient.

Prophylaxis. The prevention of attacks lies in the problem of aborting the common cold. As suggested by Poulton, the introduction of liquid paraffin in excess into the nasal passages will often abort the condition completely. Ammoniated quinine flavoured with syrup of ginger or lemon and diluted with water is reputed to abort an attack.

BUBO (Climatic bubo). See page 1009.

BURNS. These are common accidents in daily life. From the standpoint of treatment four stages are recognised: (1) shock; (2) acute toxæmia, (3) septic toxæmia, (4) healing.

Stage of shock. This is the first and foremost condition in which there is a general depression of all the vital functions. Small burns are those where 10 per cent. or less of the body surface is involved. Moderate burns are those where 10 to 30 per cent. of the body surface is involved. Severe and generally fatal cases are those where more than half the body surface is involved.

Stage of toxæmia. Here there is a rise of temperature, increased pulse and respiration rates, restlessness, and vomiting. The *stage of healing* is generally protracted.

TREATMENT. *General principles.* (1) *Treat the shock.* (a) Fluids can be administered by intravenous, subcutaneous, rectal and if possible by oral routes. Normal saline combined with glucose forms the best method for such infusion. (b) Relieve the pain and check restlessness of the patient by putting him to bed and injecting morphia $\frac{1}{4}$ gr. (c) Give warmth to the body in the form of an electric bath.

(2) *Tannic acid treatment.* The basis of modern treatment of burns is coagulation of the injured surface by tannic acid. This method has important local and general effects. Locally it is analgesic; pain, discomfort and frequent dressings are avoided on account of the presence of the coagulum. In superficial burns, sepsis is absent and healing is rapid. General effects are that it lessens fluid loss from the body at the burnt area. It probably helps by its analgesic effect to combat shock. It prevents or minimises acute toxæmia.

Aqueous solution of tannic acid 2.5 per cent. is sprayed over the raw surface from an atomizer and dried by a current of hot air or by an electric bath. This is repeated at hourly intervals, 7 to 10 such applications generally suffice. Otherwise a piece of lint soaked in solution, is kept over the areas till the coagulum forms. The lint is then removed and the coagulum dried.

Coagulating solutions used are : 1. (a) Aqueous solution of 2.5 per cent. tannic acid prepared by dissolving 7.5 gm. of tannic acid in 300 c.cm. of warm sterile water. (b) Acriflavine (1 in 1,000) prepared by dissolving 0.3 gm. of acriflavine in 300 c.cm. of warm sterile water. In every case freshly made solutions should be used for spraying.

2. Cleansing. The burnt areas should always be cleansed under general anaesthesia (ether ordinarily preferred). Remove all epithelium which is loose or raised by blistering by cutting with a pair of clean and sterile scissors. Swab the raw surface thus produced gently with ether or alcohol and then with hydrarg. perchlor. solution (1 in 1,000). After cleansing, the coagulating solutions are sprayed over the areas.

3. Treatment of sepsis. This is generally treated as ordinary wounds with fomentations, bath, ointments such as 2½ per cent. tannic acid or ordinary 'Bipp'.

4. Serum treatment. As a routine treatment in all burn cases anti-tetanic serum (1,500 units) is always given as soon as the patient overcomes the shock. During the stage of toxæmia and sepsis when the temperature rises high, anti-streptococcic serum 20 c.cm. should be injected intramuscularly. The repetition of such serum is determined by the reaction and general progress of the patient.

The above treatment applies to all types of thermal injuries and also for electrical burns.

CARBUNCLE. It is an extensive gangrene of the subcutaneous tissue as a result of an acute inflammation due to the invasion of pathogenic microbes, usually the *staphylococcus pyogenes aureus* or *albus*. The condition generally supervenes on slight injuries or as a result of auto-infection in debilitated individuals usually suffering from some chronic disease such as diabetes, albuminuria, nephritis, etc. and in whom the body resistance is low. The sweat glands and the hair follicles of the part are primarily infected with organisms; the blood supply of the subcutaneous tissues is poor and very often predispose to the condition. Though carbuncles may form on any part of the body, the common sites are the nape of the neck, the back and the buttocks. The disease is common in males over forty and appears as a hard painful infiltration of the subcutaneous tissue; the overlying skin becomes red and oedematous; the swelling increases in size peripherally and the centre becomes soft and boggy. Multiple openings gradually appear on the surface resulting in a cribriform condition of

the cutis. Many of these coalesce producing a central crateriform opening under which the necrotic mass lies. A constitutional disturbance of an asthenic type occurs; the temperature varies with cases and a temporary glycosuria of toxic origin is often present. The prognosis is usually grave in cases of carbuncles of the face and upper lip as the infection may extend and lead to intracranial complications.

TREATMENT. The general treatment of carbuncle is the same as of an acute infection. The treatment of associated primary conditions, namely, diabetes or albuminuria is as important as the disease itself. Septic foci in the body should also be eradicated. In the early stages, Bier's hyperæmic treatment, once a day (the suction cup being applied six times in three quarters of an hour with regular intermission of two or three minutes) may be successful in preventing suppuration. Locally relief is always obtained by applying a hot fomentation over a dressing of perchloride of mercury (1 in 4,000) or magnesium sulphate compresses. A thin paste of magnesium sulphate cream (magnesium sulphate 24 oz., phenol 1 dr., glycerine 12 oz.; heat magnesium sulphate to 100°C, powder while hot and add glycerine and phenol gradually) is applied over the carbuncle. Where the inflammation is spreading without definite localisation of the necrotic mass and in all carbuncles of the face, drastic operative measures should never be encouraged. Operative treatment aims at the total excision of the diseased mass. When gangrene of the part occurs and toxæmia is intense, the dead area should be immediately excised under a general anaesthetic and the cavity curetted till healthy tissue appears. The after care of the wound is the same as that of ordinary surgical wounds. Later on, nutritious food, tonics and a change of climate are advisable to aid a speedy recovery. For vaccine therapy see page 773. Light and Sosman advocate X-rays for the treatment of carbuncles. The benefit lies in a hastened necrosis of the lesion, and a softening or liquefaction of the carbuncle in the indurated stage. Sometimes the spreading tendency of the lesions is checked and healing occurs by drying up and absorption without any extensive drainage of the necrotic materials. X-ray therapy is of benefit following surgical procedures which fail to check the spread of the carbuncle and in these the activity of the infectious process is diminished and the peripheral spread stopped. Relief of pain occurs in cervical carbuncles especially in those of the face.

CEREBROSPINAL FEVER. See page 888.

CEREBROSPINAL FLUID. The cerebrospinal fluid originates from the choroid plexus in the brain. The pressure of the fluid is the same as the venous pressure, but it is considerably less than the intracranial arterial pressure (about one-sixth). The flow of the fluid can be reversed back into the blood stream by increase of the osmotic pressure of the blood as in dehydration or intravenous injection of concentrated salt solution. In meningitis the capillary cells of the plexus are disorgan-

ised and allow the protein constituents to pass into the cerebrospinal fluid. The fluid passes out from the fourth ventricle into the cisterna magna. Here the course of the fluid divides, four-fifths going over to the brain and one-fifth round the spinal cord. Blocking of the fluid produces internal hydrocephalus.

Absorption of the fluid occurs by osmosis through the arachnoid villi. The diffusion into the blood keeps pace with the formation of the fluid because the total content of salts and other electrolytes in the blood is greater than that in the cerebrospinal fluid. In meningitis the absorption is less rapid and the pressure of the spinal fluid is increased. Repeated lumbar punctures and drainage are therefore practised to bring the pressure and amount to normal. Lumbar puncture is nowadays commonly resorted to for ascertaining the character of the cerebrospinal fluid in normal health and disease, for relieving its pressure in cases of increased subdural pressure, for intrathecal administration of drugs in disease and for the collection and subsequent biochemical and pathological examinations of the fluid in the diagnosis of meningitis, intracranial hæmorrhage, convulsions, coma, persistent vomiting and syphilitic lesions of the central nervous system, *e.g.*, tabes, dementia paralytica, cerebrospinal syphilis.

Normal cerebrospinal fluid. (Values are in mgm. per 100 c. cm. unless otherwise noted). Total quantity 100 to 150 c.cm.; alkali reserve 58 to 83; specific gravity 1.007 to 1.009; pH (fresh) 7.4, pH (on standing) 8.3, pressure 7 to 9 mm. Hg. or 95 to 120 mm. H₂O, 5 to 7 mm. Hg. in children; serum albumin about 4; serum globulin 20 to 30; urea 15 to 30; creatinine 0.7 to 1.5; dextrose 70 to 100; chlorides 720 to 750. The normal cerebrospinal fluid is as clear as water. Turbidity or colour means abnormal condition. The sugar content is always diminished in all conditions of acute suppurative meningitis; it is also slightly diminished in syphilitic lesions of the central nervous system (Hopkins). It is increased in diabetes mellitus. The chloride content is increased in nephritis and decreased in meningitis, particularly in the tuberculous type (500 mgm. per 100 c.cm. of the fluid or sometimes even less). The non-protein figures are usually high in uræmia and in other nitrogen retention cases (100 mgm. to 500 mgm. per 100 c. cm. of the fluid).

Colloidal gold reaction. Lange noted that the addition of electrolytes such as NaCl to solutions of colloids such as gold effected a precipitation of the colloids, but such precipitation is also avoided by adding certain other colloids to the solution. Normal cerebrospinal fluid possesses this property, but Lange showed that fluids derived from pathological subjects cannot prevent the precipitation on adding an electrolyte. It has also been found that precipitation occurs with fluids derived from cases of general paralysis, general syphilis of the central nervous system and a few cases of meningitis. With proper technique, the three lesions can be individually differentiated.

There are three types of response—the paretic, luetic, and meningitic, varying with dilutions. A paretic response is obtained with general paralysis, and luetic responses with tabes dorsalis and cerebrospinal syphilis, while opinions vary regarding the proper interpretation of meningitic responses.

Globulin test. Normally the cerebrospinal fluid contains only a trace of protein, but the amount increases in certain pathological conditions as in meningitis and cerebrospinal syphilis; such increase, particularly the globulin content, is detected by the following test.

Technique. About one c.cm of cerebrospinal fluid is added very slowly to the same amount of saturated solution of ammonium sulphate and if there is an increase of globulin, a grey ring is formed at the junction of the two. This is the first phase of the reaction. The second phase consists in filtering off the precipitate and adding a drop of 10 per cent. acetic acid, then boiling the mixture. The formation of a precipitate indicates the presence of albumin. This last reaction is of little diagnostic value except in cases of non-syphilitic meningitis.

Loculation syndrome. The chemical changes in the cisternal and lumbar puncture fluid are of diagnostic value and constitute the syndrome. The fluid stagnates below on obstruction in the spinal cord and the following changes are found:—(1) Increase of protein up to 3 or 4 per cent. (normal being 0.02 per cent.). (2) Xanthochromia due to mixture with the fluid of the extravasated blood pigments from the congested meningeal vessels. (3) Spontaneous clotting due to increase of the fibrinogen element in the fluid. The above changes sometimes are known as 'From's syndrome' but From described a pleocytosis in the fluid as a characteristic feature, rather than an increase in the protein. The removal of the cerebrospinal fluid is of greatest value both diagnostically and therapeutically. Lumbar puncture was the only method adopted for the purpose, but now other situations may be utilised also.

VENTRICULAR PUNCTURE. It is a difficult operation for which considerable skill and special knowledge must be available. The main cavity of the lateral ventricle is situated close to the middle line and about 4 or 5 cm. in front of the upper end of the Rolandic fissure. It may be reached by puncturing the skull with a drill and introducing the needle 1 cm. from the middle line, and directing it downwards and slightly outwards.

CISTERNAL PUNCTURE. Theoretically, the ideal place for obtaining cerebrospinal fluid is one or other of the lateral ventricles because there the fluid is formed and is found in the greatest quantity, but to enter the chamber is difficult at an age when the anterior fontanelle has closed. This operation is undertaken in cases of inoperable cerebellar tumours, for the relief of severe headache and vomiting as well as threatening blindness, and injection of drugs and various other substances into the ventricles as for ventriculography. The cisterna magna (cisterna cerebello-medullaris) is the next largest collection of cerebrospinal fluid

and its drainage was first performed by an open operation by Parker in 1893. Cisternal puncture is formed when lumbar puncture is impossible owing to some spinal deformity, when repeated lumbar punctures fail to yield fluid, which may be either due to faulty technique, or occlusion of the subarachnoid space by post-inflammatory adhesions or tumours above the puncture level; when the lumbar puncture fluid is mixed with blood from injury of the venous plexus in the vicinity and where the cerebrospinal fluid is urgently needed for chemical and cytological examination and lastly the operation is helpful in localisation of spinal tumours (myelography). In cases of coma from hypnotic drugs, particularly with the barbituric acid group, Purves-Stewart and Willcox found that while lumbar puncture failed either to reduce the drug-concentration of the fluid or to rouse the patient, cisterna puncture not only reduced the concentration of the drug in the cerebrospinal fluid but also restored the patient to consciousness and brought about a cure. Similar treatment is also indicated in cases of coma due to endogenous toxins as in uræmia and eclampsia. In meningitis, the introduction of sera into the subarachnoid space of the brain through a cisterna puncture is more efficacious than through a lumbar route.

Technique. The patient is either sitting up or lying on one side. The tip of the spinous process of the axis is felt and after sterilizing and anæsthetizing the skin a graduated cisterna puncture needle is inserted in the middle line, just above the tip. It is then pushed forwards and upwards in the direction of the line joining the external auditory meatus with the glabella. A slight increased resistance is felt when the atlanto-occipital ligament is reached at a depth of 4 to 5 cm., and pushing the needle slightly forwards the cisterna cerebello-medullaris is reached. It must be noted that the medulla oblongata is situated about 2.5 to 3 cm. from the atlanto-occipital ligament and there is very little chance of any accident happening if the needle is never pushed beyond the 6 cm. mark.

LUMBAR PUNCTURE. The technique is simple. The skin at the level of the third and fourth lumbar interspace (the spinous process of the fourth vertebra is on a line joining the highest points of the iliac crests) is carefully sterilized. The patient sits up or lies with his body well flexed. A stout lumbar puncture needle is then inserted in the fourth interspace, either in the middle line or one-third of an inch from it; it must be pointed forwards with a slight inclination upwards. If the bone is encountered, the needle must be withdrawn and reinserted at a slightly different angle. In cases of repeated failures, the third interspace may be tried. In the adult the canal is reached at a depth of 2 to 2½ inches and in children 1 to 1½ inches.

Contra-indication for lumbar puncture is tumour at the base of the brain as release of the fluid may result in a sudden pushing down of

the brain on the medulla causing cessation of respiration and other vital functions.

After the puncture the patient should drink sufficient water during the following few hours and remain in a horizontal position for 12 hours. Severe headaches following lumbar puncture are not uncommon; an intramuscular injection of pituitrin by increasing the secretion of the cerebrospinal fluid promptly relieves the headache in most cases; so also intravenous injection of 100 c. cm. of normal saline solution.

LIPIODOL IN SPINAL CORD COMPRESSION. Since lipiodol was introduced in 1921 by Sicoid of Paris, considerable use has been made of it for the localization of the level of subarachnoid block. Although a skilled neurological examination will correctly localise the level of compression, a lipiodol injection would indicate the exact site, which may be important from the point of view of surgical interference. Difficulties may arise in the interpretation of the results and it must be remembered that a false arrest of the lipiodol may occur due to meningeal adhesions.

Indications. The common indications for lipiodol injections are new growths of the vertebræ, new growths of the extra dural space meninges, nerve roots or spinal cord, inflammatory thickenings or cicatrizations resulting from traumatic hæmorrhage, and syphilitic or suppurative meningitis. In fracture dislocation of the spine or spinal caries, however, a lipiodol injection seems hardly necessary, although recommended by some authorities.

Articles required for the technique consists of a lumbar puncture needle, a lipiodol syringe to fit the needle, lipiodol, hypodermic syringe, sterile novocaine solution 2 per cent., iodine and cotton wool.

Lipiodol is a 40 per cent. solution of iodine in poppy oil and is opaque to X-rays. It can be injected by cisternal or lumbar puncture. The latter method is safer and is recommended in preference to the former by Sharp and Peterson. The patient should lie on his left side, with buttocks raised, and head and shoulders depressed. A lumbar puncture is made in the usual way, and 1 c. cm. of lipiodol injected into the theca with a lipiodol syringe. The patient is then tilted so that the heavy lipiodol may gravitate upwards. X-ray photographs are taken immediately after the injection. If the lipiodol be held up by an obstruction, the skiagrams are repeated at the end of six hours, twenty-four hours and a week, to see if the level alters. Lipiodol once introduced remains unabsorbed for a long time. As a rule, it settles down in the caudal region and gives rise to no symptoms. Sicard and Foreste (1923) state that the lipiodol does not adhere, and can be removed by lumbar puncture, if desired, after several days.

CHARACTER OF THE CEREBROSPINAL FLUID IN PATHOLOGICAL CONDITIONS

Type of case	Amount easily removed and pressure in mm. H ₂ O	Cells per c.mm. and type	Total protein per cent.	W. R.	Colloidal gold reaction	Reaction pH	Urea, mgm. per 100 c.cm.	N.P.N., mgm. per 100 c.cm.	Chlorides, mgm. per 100 c.cm.	Sugar, mgm. per 100 c.cm.
Normal	7 to 10 c.cm. (child) 90 mm. (adult) 150 mm.	1 to 5 mononuclears	0.015 to 0.03	-	-	7.45	20	25	750 to 750	100
Meningococcal meningitis	30 to 50 c.cm. 300 to 700 mm.	50 to 3,000 polymorphs	0.05 to 0.5	-	+ Meningitic curve	6	30	35	650 to 700	0 to 30
Acute anterior poliomyelitis	10 to 50 c.cm. 300 mm.	10 to 100 polymorphs, later mononuclears	0.05 to 0.2	-	-	7.45	20	25	720 to 750	100
Tuberculous meningitis	15 to 30 c.cm. 800 to 700 mm.	30 to 400 mononuclears	0.05 to 0.25	-	+ Meningitic curve	7	35	40	500	6 to 40
Loculation syndrome	Varies	Varies with cause	0.1 to 0.4	Varies with cause	Varies with cause	7.45	50	45	680	70 to 100
General paralysis	7 to 20 c.cm. 160 mm.	10 to 50 mononuclears	0.05 to 0.1	+	+ Parietic curve	7.45	20	25	750 to 750	100
Cerebrospinal syphilis	7 to 20 c.cm. 160 mm.	10 to 50 mononuclears	0.05 to 0.08	+	+ Luetic curve	7.45	20	25	750 to 750	100

CHICKEN-POX. It is an acute infectious disease characterised by a rash which appears in successive crops, each lesion passing rapidly through a papular stage to one of superficial vesiculation and subsequently to partial pustulation. The lesions ultimately desiccate with formation of scab.

The disease is of world-wide distribution and affects children mainly though adults may be affected. The incubation period is generally about three weeks. In children, the day of appearance of rash is considered to be the first day of the disease, but in adults prodromal symptoms such as malaise, pains all over the body and slight pyrexia might precede the appearance of the actual rash. The rash appears in crops on successive days; first on the trunk but it soon invades the face, scalp and proximal parts of the limbs, the distribution in case of the limbs being from below upwards, the lesion being sparse and small on distal parts.

The lesions start with macules and successively pass to papules and vesicles and ultimately end in pustules. Slight pyrexia always accompanies the appearance of the rash, though sometimes an apyrexial course is met with.

Complications such as slight bronchitis, arthritis, an acute nephritis (though rare) and nervous symptoms are met with.

TREATMENT. The patient should be always isolated in bed in the pre-eruptive and the early eruptive stage till all scabs have completely separated. An alkaline diaphoretic mixture is given along with administration of copious fluids such as barley water, fruit juice, plain water and glucose during the acute stage of the disease. Regulation of the bowels is necessary. Skin irritation may be allayed by mild dusting powders and the patient should be prevented from scratching the pocks. Hot boric compresses should be applied to inflamed parts. Crusts may be removed by starch poultices and subsequently mercurial ointment may be applied. Gangrenous varicella may be treated by warm baths (containing weak phenol solution) followed by application of lotio hydrarg. perchlor. (1 in 2,000). During convalescence a nutritious but easily assimilable diet and a tonic containing iron, strychnine, phosphates, etc., should be given. A change of climate will be beneficial if the patient can afford it.

CHOLERA. See page 854.

CIRCULATORY FAILURE. This is a state of collapse due to failure of the function of the cardiovascular system resulting in a diminished cardiac output and a fall in blood pressure. Two forms of circulatory failure are recognised, a central cardiac type with impairment of the ventricular propulsive force and a peripheral vascular type where the heart does not receive an adequate venous return. The first type is associated with myocardial damage and in the second type, a distinct lesion must be present in the peripheral vascular system, though one is

dependent on the other. Sudden impairment of the coronary circulation might also precipitate the condition.

Acute cardiac failure. Formerly acute dilatation of the heart was thought to be the chief causal factor in acute cardiac failure but electrocardiographic findings and radiological observations do not support this. Dilatation of the heart is a rather gradual process as a result of chronic continued failure. Intervention of a sudden abnormal rhythm is responsible for impaired functional activities of the ventricles. Ventricular fibrillation in which each muscle fibre is having its own rhythm and in an incoordinated manner, is a potent cause of sudden death as in angina, coronary thrombosis, during chloroform anaesthesia and in digitalis poisoning. Symptoms such as syncope, dyspnoea, cardiac pain, etc., in sudden ventricular failure have led to the recognition of the following clinical types:—(1) *Cardiac syncope.* Abrupt fall in blood pressure leads to cerebral anaemia resulting in loss of consciousness. The condition is also met with in coronary thrombosis and disturbed rhythm of the heart. Syncopal attacks are liable to occur if the ventricular rate falls below twenty a minute. In Stoke-Adams syndrome, a series of symptoms, such as faintness, a giddiness and pallor appear and may even end in complete loss of consciousness. Injection of 0.5 c.cm. of adrenalin (1 in 1000) might cut short such an attack. A long needle is pushed through the fourth intercostal space, keeping the needle close to the sternal border, until the cavity of the right ventricle is reached and a little blood is withdrawn to see that the needle is inside the cavity of the ventricle. The drug is then injected into the cavity of the heart. In sudden stoppage of the heart during chloroform anaesthesia, massage of the heart through an abdominal incision is of great value while artificial respiration is resorted to.

Cardiac failure with pain. Coronary thrombosis is the cause of sudden death in this condition. There is a severe and prolonged seizure with shock, pallor, subnormal blood pressure and temperature. Diagnosis is made by an electrocardiogram. Morphia ($\frac{1}{4}$ gr.) should be injected to relieve the pain and may be repeated if required. Absolute rest, warmth and small doses of brandy should form part of the treatment. Nitrites are useless and strychnine is of little value. Digitalis should be prescribed in cases of congestive failure and in auricular fibrillation. Intravenous administration of glucose helps in the nutrition of the myocardium of the heart. Oxygen therapy is most beneficial in dyspnoea or cyanosis. After the acute stage, rest in bed is imperative.

Acute cardiac dyspnoea. Cardiac dyspnoea is a sign of left ventricular exhaustion in hypertensive heart disease, less often in coronary disease or syphilitic aortitis. Sudden pulmonary engorgement precipitates the attack. Cardiac asthma is usually nocturnal with symptoms of cyanosis, pallor, tachycardia and rapid breathing but without bronchial spasm. Pulmonary embolism also causes sudden dyspnoea, cyanosis and collapse. Injection of morphia ($\frac{1}{4}$ gr.) combined with atropine (1/1000

gr.) is often known to relieve the distressing condition. Withdrawal of 10 to 15 oz. of blood by venesection also improves the condition and particularly in pulmonary oedema. A severe case might necessitate an intravenous injection of strophanthin (1/100 gr.). After the acute stage, prolonged rest in bed and a course of digitalis by mouth are necessary.

Palpitation. Paroxysmal tachycardia may cause faintness, dyspnoea, præcordial pain or even syncope. If the myocardium is badly damaged, acute failure may suddenly develop. The attack can be cut short by inducing vomiting or by pressing over the carotid sheath in the neck. Injection of morphia ($\frac{1}{4}$ gr.) may relieve the condition. If signs of chronic heart failure develop, complete digitalisation of the patient may be necessary. Intravenous strophanthin (1/100 gr.) is of great value in acute failure. If diagnosis of tachycardia of ventricular origin is confirmed by electrocardiogram, quinidine sulphate in 5 gr. doses is given by mouth and the dose is repeated hourly up to a total of 30 gr. or until the attack ceases. In very urgent cases, quinidine has been given intravenously.

Peripheral vascular failure. Paralysis and subsequent dilatation of the peripheral vessels resulting in stasis of the circulating blood in the splanchnic area, is the principal factor in peripheral vascular failure. The heart does not receive an adequate amount of blood to contract upon, the myocardium bears the brunt and the nutrition of the heart suffers. This vascular paralysis may be central in origin or may be due to a direct toxic action of histamine-like bodies on the vessels themselves. It is seen in surgical shock, after severe injuries, hæmorrhage in certain toxæmias and in diabetic coma; the common symptoms are subnormal blood pressure, pallor, cold extremities, sweating, sighing respirations and extreme prostration.

Clinical types. (1) *Fainting.* This is a type of transient vascular failure, the main feature is cerebral anæmia resulting in loss of consciousness. Stimulation of the parasympathetic system predominates in such a condition and the loss of consciousness is gradual. Ultimate recovery is the rule though the blood pressure keeps down for some time. It is met with both in the young healthy individuals as well as in elderly people with organic disease of the heart. Emotional stresses, fatigue, ill health and menstrual periods in women often precipitate attacks. It sets in in persons while standing and never in bed while resting as in epilepsy.

(2) *Vaso-vagal attacks or Gower's syndrome.* The onset of syncope is more gradual and more prolonged preceded by psychical disturbances like epileptic aura. As regards after-effects of the syndrome, prostration is more marked, consciousness is impaired and sometimes syncope recurs. The condition is mostly seen in the middle aged with a nervous disposition. A history of previous attacks and the absence of signs of organic heart lesions confirm the diagnosis.

TREATMENT. *Peripheral failure.* The underlying principles of treatment should be to increase the volume of the circulating blood, to restore vascular tone and to lessen cerebral anæmia. The treatment is the same as for shock; the foot end of the bed should be raised and bandaging the limbs may prevent venous stasis and facilitate venous return to the heart. The patient should be kept warm under blankets or with an electric bath, where available. Fluids, in any form, should be administered orally and parenterally, to increase the blood volume. Normal saline with glucose serves the purpose best. In cases, where hæmorrhage is a causal factor, blood transfusion is imperative. As there is no organic damage of the heart, the digitalis group of drugs are useless. Of the drugs, having a local action on the vessels, adrenalin ($\frac{1}{4}$ to 1 c. cm.) and ephedrine ($\frac{1}{4}$ gr.) occupy foremost position. Injection of strychnine may be tried and injections of postpituitary preparations are of particular value in these cases. Cardiazol-ephedrine in 1 c. cm. doses is also effective. Between the attacks, sedatives like bromides or luminal should be prescribed.

Gradual heart failure. Gradual heart failure is apt to supervene in a case of old-standing valvular or myocardial disease. In the management of such a case, the chief indication is to prevent or delay the onset of failure. In order to prevent breakdown of compensation and heart failure, the patient's mode of life must be regulated. Over-exertion is particularly to be avoided and the patient should not do more than he can do without getting out of breath and this is true for the myocardial cases particularly. At least nine hours a day should be spent in bed. The diet should be one designed to keep down body fat and fluids to a minimum and also to prevent flatulence as far as possible. It should be a dry spare diet from which articles rich in cellulose (vegetables and raw fruits) are eliminated and in which starchy foods are restricted. Crisp toast and rusks should be substituted for bread and potatoes should be taken very sparingly. The chief meal should be in the middle of the day. The most useful drug to obviate failure is digitalis. It is indicated in cases of myocardial degeneration with threatened failure (senile heart in elderly individuals) and also in cases of mitral disease with auricular fibrillation; 10 min. of the tincture of digitalis thrice daily is often effective in senile cases especially. In patients with high blood pressure, potassium iodide may be given combined with digitalis. When compensation has actually broken down and failure has supervened, the indications for treatment are:—to rest the heart by lessening its work, to remove peripheral obstruction to the circulation such as dropsy, to increase the force of the systoles and to prolong the diastoles thus improving the efficiency of the contractions and lengthening the resting time of the heart. Complete rest in bed is imperative. Diet should always be restricted in severe cases of heart failure. In such cases fluids are badly borne and milk about 2 pints a day may be allowed. Digitalis should be given in efficient doses (1 to $1\frac{1}{2}$ dr. of the tincture daily) and if there is

much dropsy, diuretics may be combined with it. The following is a useful prescription in cardiac dropsy :—acetate of potassium 20 gr., tincture of digitalis 15 min., lemon syrup 1 dr. and infusion of scopolarium to 1 oz., make it to 6 oz. and one-twelfth part to be taken with a little water every four hours. The signs and symptoms due to cumulative effects of digitalis should always be watched for in these cases. To relieve congestion of the liver, mercury may be combined with digitalis as powdered digitalis, squill and pill of mercury each 1 gr., one pill to be taken every four to six hours. Diuretin is an effective diuretic in doses of 10 gr., three times a day. Symptomatic treatment is given to allay irritability of the stomach, to promote sleep and to relieve the bowels. Vomiting may be allayed by a bismuth mixture. For the promotion of sleep there is nothing better than morphia and these patients stand morphia well. To promote the action of the bowels a mercurial at night followed by a saline purgative in the morning is very effective, particularly in cases accompanied by dropsy. Mechanical removal of the dropsical fluid by Southey's tubes or by acupuncture has to be resorted to sometimes. In cases of cyanosis, continuous inhalation of oxygen is indicated. If there are signs of engorgement of the right side of the heart, venesection and withdrawal of 15 to 20 oz. of blood should be done.

CLIMATIC BUBO, LYMPHOGANULOMA INGUINALE AND ALLIED CONDITIONS. See page 1009.

COMA. It is a state of unconsciousness from which a patient cannot be roused by ordinary means. The chief causes are head injuries, the effects of drugs like opium and alcohol, diseases such as epilepsy, uræmia, diabetes mellitus, cerebral diseases including vascular lesions, tumours, abscess of brain, meningitis and encephalitis, acidosis, malignant malaria, and terminal stage of many other diseases.

DIAGNOSIS. (1) Inquire into the previous history of the patient particularly with regard to the presence of renal and cardio-vascular disease, diabetes mellitus and epilepsy. (2) Inquire into the habits of the patient regarding alcohol and other drugs. (3) Ascertain the nature of onset of coma whether sudden or gradual, whether associated with injury of the head or convulsions. (4) Examine thoroughly the comatose patient regarding age and general build, general appearance, nature and type of the breathing, abnormal odour in breath, presence of blood on lips, other external signs of injury, condition of the pupils as to size, reaction to light, etc., condition of the cardiovascular system including blood pressure, any evidence of paralysis of the face and limbs. Test the various reflexes. Examine a specimen of urine (catheterise if necessary) for sugar, albumin, casts and ketone bodies. Do a lumbar puncture. Do an ophthalmoscopic examination of the fundus oculi for optic neuritis, albuminuric retinitis and hæmorrhages. Record tempera-

ture and save all vomits. Examine the blood, especially for malarial parasites.

Different types of coma. **ALCOHOLIC COMA.** This coma is rarely deep or complete; pupils are equal or dilated; conjunctival reflex is usually present; breath has alcoholic smell; inco-ordination of movements, but no paralysis.

Treatment. Wash out the stomach and administer stimulants. Treat according to symptoms.

EPILEPTIC COMA. History is very important, as epileptic fit precedes coma. Consciousness is completely lost, pupils are inactive to light and conjunctivæ are insensitive.

Treatment. The immediate treatment consists in loosening the patient's tight clothing, collar, etc., and removing false teeth, if any. It is useless to try and arouse the patient. If there is collapse, stimulants may be given.

URÆMIC COMA. (1) History of previous kidney disease. (2) Prodromal symptoms such as headache, nausea and vomiting. Patient is more drowsy than comatose; there may be convulsions. (3) Respiratory difficulty, breathing may be 'hissing' or Cheyne-Stokes type (Renal asthma). (4) Urine contains albumin and casts and the quantity is scanty. (5) Blood pressure may be high. (6) Blood urea and non-protein nitrogen are high. (7) Examine fundus oculi.

Treatment. Do a venesection and remove as much as 15 to 20 oz. of blood thereby reducing the amount of circulating toxin. Administer intravenously nearly the same amount or a little less of normal sterile saline with glucose to further dilute the circulating toxin. Administer normal saline with sodium bicarbonate and glucose per rectum. Do a lumbar puncture to reduce cerebral oedema. Prescribe compound jalap powder to be followed by a saline purge for free purgation. Hot air bath by electric cage for sufficient diaphoresis is needed. If the patient can swallow, prescribe alkaline mixture with calcium diuretin. Linseed poultice or dry cupping over the lumbar regions, to facilitate the secretion of urine, is useful. To control the spasm during convulsions administer a few whiffs of chloroform. Chloral hydrate and bromides are given to keep the patient quiet; nitrites are given if the blood pressure is high. Morphine should be cautiously administered to check restlessness and delirium and to prevent recurrence of the uræmic fits. Calcium lactate may be given if vomiting and hiccough are present. Diet should be very low in proteins.

DIABETIC COMA. See page 1049.

APOPLÆCTIC COMA. May be due to (a) cerebral hæmorrhage, (b) cerebral thrombosis, and (c) cerebral embolism.

Cerebral hæmorrhage. Diagnosis. History of the case, age of the patient usually 45 to 65 years. Onset is sudden and the coma is deep and progressive. The blood pressure is high and pulse is full and bounding.

The pupils are unequal and do not respond to light. There is conjugate deviation of eyes. The respiration is hurried, noisy, stertorous and may be of the Cheyne-Stokes type. Paralysis of the face, arm and leg on the side opposite to the lesion. Cerebrospinal fluid comes out under pressure and is mixed with blood.

Cerebral thrombosis. History of the case, onset is gradual, the patient is conscious; the cerebrospinal fluid does not contain blood. Occurs at early age

Cerebral embolism. Diagnosis. History. Onset is sudden; evidence of mitral stenosis, infective endocarditis or any other source of emboli; consciousness usually not lost; occurs in early life.

COMA DUE TO HÆMORRHAGE INTO THE PONS. Crossed paralysis, pin-point pupils and hyperpyrexia are present.

COMA DUE TO MENINGEAL HÆMORRHAGE. History of direct head injury, a latent period and then a coma.

OPIUM POISONING. History of the case, pupils contracted, breathing slow and Cheyne-Stokes type.

Treatment. Wash out stomach and examine contents. (See page 1453).

COMA DUE TO HYPERPYREXIA. This is an important cause in the tropics and commonly occurs in malignant malaria. Examine blood for the presence of the parasites. Coma due to hyperpyrexia after sunstroke is also common in the tropics (See page 218).

COMMON COLD. The catarrh affecting the nasopharynx, the larynx and the bronchial tubes is known as the common cold. One should not suggest a chill to be the exciting cause of the malady as has been very erroneously done by the laity. The inflammatory condition affecting the mucous membrane of the upper respiratory passages is attributed to external irritants and invasion by pathogenic bacteria. Inclement weather such as damp, cold and chill, by lowering the resisting power of the individual, very often predispose to microbic invasion of the parts. In all cases of acute common cold there is an infection by microorganisms such as the *Friedlander's bacillus*, *H. influenza*, *Bacillus septicus*, *Micrococcus catarrhalis* and pneumococcus, which may occur separately or combined. The condition is usually infectious and is very liable to pass from one member of a household to another. The infection induces inflammatory reaction and the catarrh primarily starts in the nose. Deformity and deflection of the nasal septum, the presence of a ridge or spur on the septum are causal factors, as these help in the retention of the secretions which keep up the infection. Recurrent attacks of cold in susceptible individuals render the nasal mucous membrane more susceptible to inflammatory changes. Children are more susceptible to colds than adults on account of variety of predisposing causes. The presence of adenoids is by far the commonest cause of nasal catarrh in children. Children brought up under bad hygienic conditions are predisposed to this malady. Deficient and stagnant ventilation and dusty

atmosphere also contribute a great deal towards the causation of this common disease. Any condition of faulty metabolism predisposes to nasal catarrh, but sufferers from gout, rheumatism, syphilis and diabetes, are very liable to it. In women anæmia and pelvic troubles are important predisposing factors. Neurotic individuals of the vagotonic type supply many cases.

TREATMENT. All nasal abnormalities should be corrected by surgical operation. Adenoids in children should always be removed and such measures often cure the complaint unless chronic catarrhal changes have supervened. General treatment is useless unless such abnormality is properly dealt with. As regards extranasal causes, a careful search should be made into the general health, habits and hygiene of the patient. Clothing should be such as to promote the healthy action of the skin. Some form of exercise should be enjoined by the patient before the morning bath. When the site of infection is within easy reach of drugs, it is easy to abort an early attack. This is done by washing the microbes out of the part with a weak antiseptic lotion or normal saline, which is used both as a gargle and a nasal douche. The antiseptic lotion for the nasal douche should be comfortably warm (100°F.), alkaline in reaction and isotonic with the blood plasma. A useful prescription for this purpose is bicarbonate and bborate of sodium each 4 gr., benzoate of sodium 1/6 gr., oil of eucalyptus 1/12 min., menthol 1/24 gr., and water to 1 oz.; to be mixed with warm water and used as a nasal douche. It can also be used as a gargle. An efficient early treatment will cut short the attack and prevent the spread of the infection. Dobell's solution used as a nasal douche is often reputed to abort early cases of whooping cough. The formula is bicarbonate and bilorate of soda each 30 gr., listerine 2 dr., glycerine 6 dr., and water to 1 pint. It is difficult to efficiently sterilise the parts when the catarrh starts lower down in the respiratory passages such as in the larynx. Oils such as eucalyptus, well-vaporized or atomized in a suitable apparatus and inhaled vigorously and frequently both through the mouth and nose are exceedingly useful. The household remedy of Friar's Balsam (1 dr. to a pint of hot water) inhaled from a wide-mouthed jug is very efficacious. A combination is oil of eucalyptus 20 to 40 min., menthol 10 gr. to 1 dr., liquid paraffin to 2 oz. can be used as a spray. Aqueous solutions in the form of sprays may also be used, and the following is a useful prescription:—bicarbonate and bborate of sodium each 5 gr., liquid carbolic acid ½ min., glycerine 20 min., and water to 1 oz., this is to be freely sprayed through the nostrils into the throat every four hours through an atomizer. In case of an acute attack rest in bed for a few days is imperative. During this time a mild mercurial purgative such as calomel in divided doses, followed by a saline aperient in the morning is very helpful. When constitutional disturbances such as headache and fever are present, Dover's powder 5 to 15 gr., or preparations of quinine are of special value. Quinine is said to be a general tonic after a cold

and the drug is sometimes taken as an effervescent mixture. A useful formula is: (A) Sulphate of quinine $2\frac{1}{2}$ gr., citric acid 10 gr., water to $\frac{1}{2}$ oz. (B) Bicarbonate of potassium 10 gr., carbonate of ammonia $2\frac{1}{2}$ gr., syrup 1 dr., and water to 1 oz. A tablespoonful of (A) to be added to two tablespoonfuls of (B) and taken while effervescent. Sedative expectorants are most effective during the acute congestive period when the cough is hard and accompanied by slight mucus. It is only when the congestion is relieved and the secretion is free that stimulating expectorant drugs should be prescribed. When the muco-purulent exudation is mainly tracheal cubebs are held to be efficacious. The usual dose is 20 gr. of the powder given for the treatment of harassing cough.

As a local measure wool tampons in the nostrils impregnated with menthol and formalin relieve the obstruction and when the secretion is free a nasal douche is advisable. An oily solution containing thymol 3 gr., camphor 4 gr., menthol 10 gr., oil of cinnamon 4 min., liquid paraffin 1 oz. may be used in an atomizer for a spray inside the nasal cavity in case of swelling and irritation of the mucous membrane. A hot bath or a hot wet pack is very useful in the treatment of the common cold. The underlying idea is to induce copious perspiration by such processes. Two or even three of these packs may be given in a week. The diet in the acute stage of the disease should be liquid; an active preparation of vitamins B, and D are useful adjuncts in the dietary. Ultra violet rays have been suggested by some to be efficacious in acute and chronic catarrh both locally and generally. For vaccine therapy see page 773.

Following are useful prescriptions in common cold:—

Chlorine mixture. Chlorate of potassium 50 gr., hydrochloric acid 30 min., syrup $\frac{1}{2}$ oz. and water to 1 oz. Allow the chlorate to stand in contact with the acid in a stoppered bottle for ten minutes and then add some water and shake. The dose is two or three dr. in 1 oz. of water for an adult. It should not be given more than three times a day lest methæmoglobinæmia may supervene.

Coryza mixture. Salicylate of sodium 6 gr., compound tincture of chloroform and morphine 5 min., chloride of ammonia 5 gr., compound tincture of cinchona 1 dr., tincture of catechu 15 min., syrup of tolu 30 min., liquid extract of nux-vomica $\frac{1}{2}$ min., lemon syrup $\frac{1}{2}$ dr., glycerine 15 min., and water to 1 oz. The mixture should be kept in the dark and though the dose is 1 oz. it is better to take $\frac{1}{2}$ doses frequently after a few full ones.

Chloretone nebulant. Chlorbutol 15 gr., camphor 37 gr., menthol 37 gr., cinnamon oil 4 min., light liquid paraffin to 4 oz. To be sprayed frequently with an atomiser.

CONJUNCTIVITIS. Inflammation of the conjunctiva may be acute or chronic. It is due to a variety of causes such as smoke, irritant vapours, trauma, errors of refraction, etc. It also occurs in certain

constitutional diseases, but the most important is one of microbic origin, the common organisms being pneumococcus, gonococcus and certain bacilli. Conjunctivitis should therefore be considered as an infectious disease. The common symptoms are gritty sensations, photophobia, a purulent discharge and sticking of the eyelids in the morning.

TREATMENT. The diseased eye should never be bandaged, as the discharge should have a free drainage. Free lavage of the conjunctival sac should always be encouraged with a bland, non-irritating weak antiseptic lotion. Ordinary sterile, tepid, normal saline serves the purpose best, though boric lotion (10 gr. to an oz.), perchloride of mercury (1 in 5,000), Condy's fluid (1 in 2,000), etc., are also used. Irrigation of the diseased conjunctival sac should be repeated as often as possible, specially where a purulent discharge is present. Of the drugs prescribed as eye lotions zinc sulphate ($\frac{1}{2}$ to 1 per cent. or 2 gr. to an oz., argyrol (20 to 25 per cent.), protargol (2 to 5 per cent.), silver nitrate (1 to 2 per cent.) and tannic acid (1 per cent.) are most commonly used. Some are irritating and the selection of such drugs should be made to suit individual cases. Argyrol is very commonly used nowadays in the treatment of the common forms of conjunctivitis.

A few common types of conjunctivitis. (1) *Acute catarrhal conjunctivitis.* This is a muco-purulent type of conjunctivitis, the exciting cause is the pneumococcus. Argyrol should be prescribed in the form of eye-drops, three times a day early in the affection and later on zinc sulphate is used. If there is sticking of the eyelids on waking in the morning ointments of yellow oxide of mercury ($\frac{1}{2}$ to 1 per cent.), perchloride of mercury (1 in 3,000) or boric acid (B. P.) may be applied to the conjunctiva at bed time. (2) *Gonorrhœal ophthalmia.* The exciting cause of this type of conjunctivitis is the gonococcus and when seen in the new-born it is called *ophthalmia neonatorum*. The routine method of treatment in maternity practice is to instil drops of silver nitrate (1 per cent.) in the eyes of the new-born infant where infection is suspected. Free lavage of the conjunctival sacs with Condy's lotion (1 in 4,000) should be advised. Silver nitrate (2 per cent.) solution should be applied every morning to the everted lids which should be always kept clean and dry. It is highly infectious. (3) *Trachoma.* This is a very chronic form of conjunctivitis. The main treatment consists in the application to the everted lids of 2 per cent. silver nitrate in the early stages and of copper sulphate stick in the later stages of the disease. This should be done three times a week. It is also highly infectious. (4) *Phlyctenular conjunctivitis.* This is seen in debilitated children and the disease often runs a chronic course. Application of yellow oxide of mercury (1 per cent.) as ointment or dusting of calomel powder, once a day to the phlyctenules of the eye, is beneficial. The pupils should always be dilated with atropine ointment (1 per cent.) where the cornea is involved. The general condition of the patient should be improved with fresh air, nutritious and assimilable food, tonics and cod liver oil.

CONSTIPATION. It is essentially a functional disorder of the large gut and so is only a symptom, but the condition is so common that it is almost considered as a disease in itself. The treatment of the condition is more important as it is such an important aetiological factor in the development of so many chronic diseases that may lead to a fatal issue. Chronic intestinal stasis is also held responsible for the development of the symptom complex of auto-intoxication. Before adopting any special method of treatment either with drugs or with other recent physical agents, investigate thoroughly into the causes of the condition. The treatment of constipation properly considered is essentially a treatment of the patient himself rather than that of the disease, so that a careful and close scrutiny has to be made regarding his general habits, the quantity, quality and frequency of meals, any previous intestinal diseases, and the general muscular state and build of the patient. In the case of female patients, in addition to those already mentioned an enquiry should be made into the obstetrical history of the patient along with other associated symptoms.

In diagnosing the definite cause of constipation, the three types of colon with characteristic features have to be considered as the line of treatment differs accordingly.

Spastic colon. This is a vagotonic state of the large gut. The descending colon is hard, rigid, contracted and tender. The part is extremely irritable due to over purgation, faulty dietary, undigested irritating food particles and the spasticity is sometimes secondary to a septic focus elsewhere. Here constipation is irregular and response to purgatives is uncertain. The patient suffers from colicky pains and gaseous distension of the gut. The stools contain an excess of mucus and are sour smelling due to fermentation of food materials. *Atonic colon.* This state of the large bowel is seen in middle-aged people with neglected health. The abdomen is lax and pendulous. The constipation is persistent and motions are offensive due to caecal stasis and putrefaction of the protein portions of the diet. The diet also in these cases consists of a greater percentage of proteins which offer a poor stimulus to the colonic activity. *Dyschezia.* Hurst regards this to be a rectal condition, often associated with atonic colon, due to a failure of response to the desire for defaecation. The rectum is inattentive to the faecal mass and does not, in these cases, exert itself to evacuate its contents. Such a condition is generally associated with muscular damage, abdominal or perineal, or is due to some local conditions such as the presence of haemorrhoids or a growth which render defaecation painful and uncomfortable. Generally women with poorer musculature and sedentary habits suffer more than men. A local examination of the rectum in these cases is most essential before other causes are excluded.

Radiograms are very helpful in diagnosing these conditions after a barium meal and also detecting other local conditions such as new growths in the colon or rectum.

Acute constipation. In acute obstinate constipation of a few days' duration and in the absence of any mechanical obstruction or inflammation, a pint or two of an ordinary soap-sud enema should in the first instance be always tried and, if no results follow, a compound enema consisting of castor oil, olive oil, tincture asafetida and oil of turpentine, followed again by another soap-sud enema sometimes gives encouraging results. This routine is of particular value where the abdomen is bloated due to gaseous distension of the coils of intestine. Injections of eserine or physostigmine sulphate have also been tried as a last resort in cases of acute constipation due to paralytic ileus and similar conditions. A full dose of castor oil is also worth trying in these cases.

Chronic constipation. In chronic constipation with signs and symptoms of autointoxication due to intestinal stasis, thorough irrigation of the gut is most helpful. Long-continued physical therapy with appropriate medicinal treatment and diet therapy are all that are needed for the treatment of such conditions. Habitual constipation is also a type of chronic constipation and the secret of treatment lies more in correcting personal habits and dietetic errors of the patient than by treating with ordinary purgative drugs. Laxatives like milk of magnesia, senna and liquorice powder at bed time followed by a small dose of an effervescing draught in the morning are helpful in these cases. No purgative drug should be taken for a long time.

In the atonic type of constipation, increase and maintenance of tone and contractility of intestinal muscles should be aimed at. Physical therapy is useful and sinusoidal currents are more beneficial in these cases than the treatment with drugs. A pill consisting of strychnine, aloin and belladonna is often prescribed in these cases. Increase in mass and fluid should precede an actual stimulation of the gut and salines may serve the purpose.

The spastic colon calls for atropine to normalize the function of the gut and the drug should be continued for some time. Vegetable purgatives, asafetida and benzyl-esters are also beneficial in these types.

Mineral oils are of special service when secretions are lacking and are very useful in all cases of stasis whether spastic, atonic or dependent on anatomic fault. In dyschezia, correct all local errors, if any, of the rectum. Of the purgative drugs, liquid paraffin, agar agar, senna, liquorice powder are often prescribed. The former two lubricate and facilitate the passage of the bowel contents and defæcation is no longer painful. Before instituting any line of treatment, a local examination of the rectum is most essential.

DIET THERAPY. Diet is the most important ætiological factor in the causation of constipation and is probably responsible for it in the majority of cases. A correction of dietetic errors with the institution of a proper diet therapy go a long way towards curing the condition,

particularly in chronic habitual constipation. In chronic constipation, physical therapy should go hand in hand with diet therapy and drugs should come in occasionally.

A complete and thorough enquiry is to be made into the food intake of the individual, its frequency, quantity and quality. The prescribing of a proper diet varies with the types of cases and so a case history is most important. In the atonic type, stimulation of the gut is necessary and hence the bulk of meals should be increased. The coarser cereals, brown bread, fresh green vegetables, salads, fresh fruits be taken in abundantly for this purpose. The daily fluid intake should also be large. The protein intake should be reduced, to limit putrefactive processes inside the gut. The supply of vitamin B and its storage inside the body should be freely encouraged in the treatment of these cases. In the spastic type of case, the intake of roughage is unsuitable, as it is not desirable to stimulate any further an already irritated bowel. Tough, stringy meat, coarse vegetables, fruits with pips and skins should always be avoided while the softer forms of meat, simpler fruits and vegetables are allowed in their place. Sugars favouring fermentation should be reduced. Feeds should include a liberal supply of dairy products, milk, citrated if necessary, cream, raw or lightly boiled eggs and butter, the idea being to soothe the bowel.

In dyschezia, increase in mass and quality should be aimed at. Feeds of a soft, oily and lubricant nature, such as butter, cream and fats should be taken abundantly. Proteins should be reduced with a corresponding increase in carbohydrates like cereals, potatoes, bananas and other forms of starch. The idea here is to lubricate the passage during evacuation of the contents of the gut.

PHYSICAL THERAPY. The co-operation of the patient with the practitioner is desirable in correcting the faulty personal habits of the individual. It is not sufficient to cleanse the bowel only once, but it must be kept clean to avoid subsequent complications following intestinal stasis. The necessity of a complete and thorough evacuation of the bowel, daily, cannot be overestimated. Hurries and worries of daily life are direct hindrances to response to the call of nature and these with other factors have sometimes deleterious effects on the intestinal activities of the individual. The intake of a tumblerful of cold water on waking in the morning sets off a gastro-colic reflex necessary for the purpose. The tone of the abdominal muscles should be improved both in young and elderly people with suitable exercises and massage. Sometimes the sitting posture at stool is faulty and this should be corrected. The intestines are slung from the back and a better adjustment and co-ordination of all the forces concerned in the act of defaecation are served only when the body is bent forwards or if possible, when one rests with the elbows on the knees.

The development of physical therapy in diseases is of recent origin and so also its application to the treatment and prevention of constipation. This line of treatment is of particular value in habitual chronic constipation where drugs and other therapy fail to correct the condition. It is also useful to convalescing patients or individuals with lax and pendulous abdomens where muscular effort is much reduced during the act of defæcation. Physical therapy only attains success in the hands of experts.

Massage. Abdominal massage and exercises for abdominal muscles have been practised for years and the technique has been improved and developed in the hands of Ling, the founder of the Sweedish system of exercises. Along with massage proper diet therapy should be advised and the correction of other faulty habits of the individual should be aimed at as all these combined go a long way in curing chronic obstinate types of constipation. The massage of the abdominal wall is said to stimulate the sympathetic system and indirectly it promotes the tone of the intestinal muscles. The masseur should also pay some attention to the muscles of the back and pelvis. Results have been encouraging with simple massage of the part not lasting more than a quarter of an hour each time and repeated four times a week.

Special types of massage recommended for the purpose are (a) Colonic self-massage. (b) The folding exercise. (c) The pulling type. Regarding the details of the above types of massage, special treatises dealing with these should be consulted.

Exercise. In the tropics, the enervating influence of the climate makes people more ease-loving and they are quickly fatigued with a less amount of work than people inhabiting countries in the temperate zone. Though Indian types of exercises are varied and interesting, very few take them regularly. As people grow old, they give up all sorts of exercises and settle down to a sedentary life, thereby making a good base on which constipation can develop. They are often obese persons with a lax pendulous abdomen and without power of exerting the abdominal muscles during defæcation. Women folk in the tropics suffer most and of these particularly 'pardaneshin' ladies with sedentary habits. Damages to the perineal muscles and other accessory muscles concerned in defæcation during repeated parturitions are also contributory causes in the later development of constipation in those women. The Western system of exercises including those of Müller and Hornibrook may not suit people in the tropics, but even such simple exercises as walking, running or swimming are not regularly practised by them. The neuromuscular system is never properly developed and with advancing years this is deranged and refuses to work properly resulting in intestinal stasis and similar functional disorders of the body system.

Electrical therapy. This is of immense value particularly in chronic types of constipation with weak abdominal muscles. Diathermy or artificial sunlight treatment is of real value and serves as a general sedative

tonic where the causal factors of constipation are overwork, worry, fatigue or illness. Regular interrupted faradic stimulation (in the form of Bergonie's chair) of the whole abdomino-perineal musculature is also a very effective form of treatment for chronic constipation. Sinusoidal current also serves the purpose where abdominal muscles have lost their tone. Of other electrical appliances used to strengthen and promote the tone of the abdominal-pelvic-genital muscles, the rhythmic myotroph, Mortin Smart or Bristow coil, deserve a mention here. Electrical therapy should go hand in hand with other forms of therapy for the treatment of constipation.

Lavage treatment. Per rectum. The keynote of this particular type of treatment is to give the bowel time to rest after clearing away the stagnant debris. Of the various forms generally practised, the German Suda chair is the best and most effective though the Plombiere's, the American Suda chair and the two way methods with their applicability in different conditions of the gut deserve mention.

Lavage by the mouth or the water regime. The patient is asked to drink two tumblers of cold water on waking in the morning. The water intake may be increased to about a quart and the patient is then asked to lie on his left side for a quarter of an hour followed by five minutes on his right side before getting up. The water may be warmed a little to suit the patient. The patient may be allowed to take the purgative drug he is used to along with it. If during the early part of this treatment, the quantity of urine passed is increased after such water intake he should be advised to lie down on his side for a prolonged period of time. This treatment has given encouraging results though the underlying rational physiological process operating is not clear. This technique of water regime had been practised by physicians in the old days in the indigenous system of medicine and it is well worth reviving in modern times with the advancement of physical therapy.

Medicinal treatment. Drugs. The list of purgatives and the proprietary drugs on the market is enormous and the difficulty and confusion are mostly experienced by practitioners in the selection of the drugs. Attempts will be made to discuss a few important purgative drugs only in the treatment of constipation and only those that are generally prescribed in everyday practice by practitioners will be described.

Paraffin group. The paraffin group of purgative drugs is most extensively used for their harmless action and the absence of after-effects. They can be safely prescribed for the aged and the young alike and even in cases of full-term pregnant women. They are useful in chronic constipation and the action is purely mechanical, as a lubricant facilitating the passage of hard faecal masses. They are never absorbed and so there is no systemic effects. They have a certain amount of antiseptic action on the bacteria of the intestine. Their action is enhanced by combining them with cascara. The disagreeable effects

are leakage of the oil when flatus is passed. Very prolonged use is said to give rise to irritation and decrease of absorption of foodstuffs from the intestine. *Dose*—1 to 2 oz.

Agar agar. It is a colloid laxative acting purely mechanically by increasing the bulk of the contents of the bowel. It is not acted upon by digestive juices and is not absorbed. As it does not actually stimulate the peristaltic activity of the gut it should be combined with other mild laxatives in the atonic type of constipation. Its disadvantages are that it retards absorption of foodstuffs and favours the growth of bacteria.

Glycerine. It is generally used for rectal injections or is used in the form of a suppository. The action is due to irritation of the mucous membrane of the rectum and the drug causes evacuation of the lower bowel. The drug suits infants and young children where oral administration of a purgative is difficult and undesirable.

Castor oil. Of all purgative drugs castor oil is most extensively used and is a common household remedy for constipation. In chronic constipation in entero-intoxication and in diarrhoea due to indigestion and dietetic errors, the drug is most useful and helpful in thoroughly evacuating the bowel of its irritating contents. The oil should not be prescribed for continuous use in habitual constipation. The oil is not generally taken, as such, on account of its nauseating taste but is given as an emulsion flavoured and sweetened with some agent. Infants tolerate the oil better than adults. Castor oil itself is inert but is saponified in the gut by bile and fat-splitting pancreatic ferment to glycerine and fresh fatty acids. The remaining unsaponified oil supports the action mechanically by lubrication. Castor oil is a safe purgative and may be given in large doses since, as soon as a sufficient quantity is hydrolysed, the resulting cathartic action carries away the superfluous oil. The action begins in the duodenum and passes down through the jejunum into the ileum and colon. It produces thorough evacuation of the bowel and is therefore prone to be followed by constipation. *Dose*—1 to 2 oz.

Croton oil. The drug is a purgative of emergency for its prompt action and is of special use in apoplectic coma, in cerebral hæmorrhage and in lead colic when other purgatives fail to act.

Mercurials. Calomel is commonly used as a purgative drug. Because of its cholagogue property, the drug is often the cathartic of choice in an attack of acute indigestion accompanied by constipation with white pasty stools, coated tongue and other signs of biliousness. The drug should always be given in small repeated doses, $\frac{1}{4}$ to $\frac{1}{2}$ gr. every half an hour as it is changed to grey oxide inside the bowel exerting its cathartic effects, but when a large dose is given at a time, a portion of it is only so changed, the rest passing unaltered or being absorbed and exerting toxic effects. Calomel acts mainly on the small intestines, its action on the large gut being mild. It has a certain amount of antiseptic action and putrefaction in the intestine is decreased by its use as shown by decrease in the bacterial content of fæces and sul-

phates in the urine. A saline purgative should always be taken in the morning to ensure evacuation of the large gut. The drug should never be prescribed for habitual constipation for its repeated use might result in pyalism and other signs of mercurial poisoning.

Anthraces. Cascara sagrada is considered to be one of the best intestinal stimulants in the atonic type of constipation. It has the special advantage of maintaining a regular effect even with continuous and prolonged use. The main therapeutic action of the drug lies in improving the tonicity and excitability of the intestinal musculature. Griping after its use is rare and the tendency to after-constipation is slight. The dose can be slowly reduced tailing off finally to cessation. It may be safely prescribed even to pregnant women nearing term. Several palatable preparations are sold to suit the taste of patients and of these cascara evacuant (P. D. & Co.) is well-known. A teaspoonful in the evening produces the desired result in the morning.

Senna. It is a commonly used and useful vegetable cathartic producing copious stools in 8 to 10 hours. In habitual constipation, an infusion of senna pods (6 to 10 pods left overnight in a glassful of cold water) is an effective preparation evacuating the entire bowel without griping. The drug causes griping when prescribed alone and hence it is often prescribed with ginger, cinnamon and similar carminatives to prevent this. Senna mainly acts on the large intestines. Pulv. glycerrhiza compound contains this drug and sulphur and is specially advised for pregnant women and in cases of hæmorrhoids where ordinary defæcation is painful. It is best taken at night to act in the morning.

Rhubarb. The drug is more an astringent, bitter and stomachic tonic than a cathartic. It causes an evacuation of the offending putrefied foodstuffs due to indigestion, from the bowel and later on controls the diarrhoea by its astringency.

Aloes. The drug has limited applications. It should never be given in cases of hæmorrhoids and pregnancy as it produces a congestion of the sigmoid colon, rectum and the pelvic organs in females. It is especially useful in overcoming the constipation of hypochondriasis and melancholia. The action of the drug is slow and it causes griping.

Hydragogues. They are not common remedies against simple constipation. These drugs are particularly useful in general anasarca of the body, in dropsy of cardiac or hepatic origin, in congestive or inflammatory states of the meninges, cerebral congestion and hæmorrhage. Jalap causes griping and has constipating after-effects. The action of these drugs is too severe for them to be given alone and so they are prescribed in conjunction with other purgatives in various cathartic pills.

Salines. Salines are very commonly used in habitual constipation by elderly people in the form of some sort of effervescing drink on

waking early in the morning. These act by altering osmotic tension and increasing fluid retention or reducing its absorption from the gut. Salines should be followed by intake of a copious amount of plain water so as to increase the bulk.

Magnesium sulphate. It is a common household remedy and is an efficient evacuant producing several watery motions without any griping. The drug is of particular value in cleansing the bowel of offensive and poisonous materials, relieving cerebral congestion or general anasarca of the body. It is also used in cases of acute food poisoning, and indigestion. In lead colic, a prescription containing magnesium sulphate 1 oz., morphine sulphate $\frac{1}{4}$ gr., dilute sulphuric acid 30 min., and peppermint water up to 4 oz. is very useful. One tablespoonful of this with an ounce of water to be taken in every hour till free purgation sets in.

Atropine. The drug is most reliable and specially reputed for its specific vagotropic action and is very useful in the relief of spastic states of the intestine where the vagus is overactive. The drug tends to normalize the tone and contractility of the gut and cuts short the irregular spasms of the intestinal muscles. The pure drug is superior to belladonna and the commencing dose should not exceed 1/150 gr. and be repeated three times a day.

The importance of treatment of constipation in the tropics with so many varying ætiological factors cannot be over-emphasized. No hard and fast rules can be laid down for its treatment. The treatment essentially depends on the merits of the case. 'Treat the patient and not the condition' should be the idea of the practitioner. Drugs only help and probably very seldom cure such conditions. Correction of personal habits and the institution of appropriate diet and physical therapy are all that should be aimed at by general practitioners in laying down a general line of treatment of constipation.

Convulsions in children. The causes of convulsions are : (1) violent diarrhoea and vomiting, (2) in any pyrexia and corresponding to what would be a rigor in an adult. Older children are liable to fits at the onset of lobar pneumonia, pyelitis, or tonsillitis; (3) rickets especially between ages of one and a half and three years, (4) teething, phimosia and worms; (5) sometimes in congenital syphilis; (6) convulsions are common in tuberculous or meningococcal meningitis; (7) tetany (note Chvostek's signs) which may be stopped by injection of 1 per cent. calcium chloride solution intravenously. Chloral and bromide will prevent recurrence.

When the child is in a fit : (1) Try to check the convulsions. Put the child in warm bath and sponge its head with cold water and artificial respiration by gently squeezing the chest with the hand should be resorted to. Inhalation of ammonia is also beneficial; (2) prevent recurrence by potassium bromide in plenty of water, and (3) lastly investigate the cause and treat accordingly.

In adults convulsions may or may not be accompanied by loss of consciousness. (A) When consciousness is retained the causes are, (i) poisoning by drugs like strychnine, (ii) Jacksonian epilepsy, (iii) tetanus, and (iv) tetany.

(B) When consciousness is lost the causes of convulsions may be, (a) epilepsy, which may be treated by injection of sodium luminal 5 gr., or apomorphine 1/6 gr.; (b) Stokes Adam's disease, in which case intracardiac injection of 5 min. of adrenalin has given hopeful results, followed by subcutaneous injection of adrenalin four times a day or barium chloride 1 gr. by mouth three times a day to prevent recurrence, (c) poisons other than strychnine such as cocaine, chronic alcoholic poisoning, etc.; (d) cerebral hæmorrhage; (e) uræmia; (f) general paralysis of insane; (g) hypoglycæmic condition due to overdose of insulin (for treatment see page 1049); (h) eclampsia which is treated with chloroform, liquid glucose, etc.

Emergency treatment of fits accompanied by coma. (1) Prevent the patient from hurting himself, (2) do not attempt to hold him down, (3) put something between his teeth so that he may not injure his tongue, (4) loosen clothing and start artificial (Schafer's) respiration, (5) when convulsion ceases give large doses of potassium bromide in water to prevent recurrence of fits.

COUGH. It is one of the cardinal symptoms of the diseases of the respiratory system and is a valuable diagnostic sign of many diseases of grave prognostic importance. The common causes of cough are enlarged tonsils, adenoids and long uvula particularly in children, pharyngitis associated with dyspeptic conditions, laryngitis, and tracheitis. The coughs arising out of conditions affecting the lungs and pleuræ are those of acute and chronic bronchitis, acute pleurisy, pulmonary emphysema, bronchiectasis, pulmonary tuberculosis, fibrosis of the lungs and pulmonary neoplasms. The nature of the cough should always be studied as it gives a clue to the diagnosis of the particular disease, and proper treatment in time may save the patient from long years of suffering. The tonsil and adenoid cough is of a dry nature, the long uvula cough is also of a dry nature and occurs at night when the patient is in bed. The pharyngitis cough due to dyspeptic conditions tends to occur chiefly in the morning and is non-productive. The laryngitis cough is raucous in character, painful and often associated with hoarseness. In tracheitis, the cough is severe and is totally out of proportion to the physical signs found in the chest. The cough of acute bronchitis is painful and non-productive, of chronic bronchitis it is painless and associated with copious expectoration of mucoid and mucopurulent sputum. The cough in acute pleurisy is most painful, short and dry and is particularly common in the early stages of pneumonia when the pleuræ are involved. In pulmonary emphysema it is associated with a marked degree of dyspnoea and is non-productive.

It is paroxysmal and simulates a condition of asthma. The cough of early tuberculosis is dry and non-productive, and the presence of expectoration suggests that ulceration of the lung has taken place. When the tuberculous disease has advanced to the state of cavitation the cough becomes paroxysmal in nature and the patient attempts to empty the cavity. This type of cough is also met with in advanced bronchiectasis. The cough is almost incessant in cases of new growths in the lungs. In the early stages it is dry and hacking and later on associated with hæmorrhagic sputum. In cases of cardiac dilatation, the cough is painful and entails an effort on the part of the patient. The cough in cases of enlarged mediastinal glands, mediastinal neoplasms and aneurysm is paroxysmal in nature and later on it is of a mild type but irritating, persistent and non-productive. The true brassy cough is always a diagnostic feature of severe degrees of pressure. The reflex causes of cough include some local irritation in the ears or teeth, disorder of the gastro-intestinal tract, pericarditis and genito-urinary diseases in women, or after abdominal operations. It is dry, persistent and non-productive. The most important reflex cough in the adult is due to dyspepsia associated with a pharyngitis and it is typically a morning cough and is relieved by a large and copious expectoration. The habit cough of heavy smokers is familiar to all. The nervous cough is usually of a barking nature and is more distressing to others than to the patient. It is non-productive and is generally associated with nervous diseases. The hysterical cough is still more harassing and may be associated with hæmoptysis.

A thorough investigation into the personal and family history of the patient with a careful physical examination of the chest considerably helps the diagnosis. Skiagrams of the chest often detect hidden lesions. A local examination of the oral cavity, throat and the accessible portions of the pharynx and larynx should be made before the treatment is adopted.

TREATMENT. A correct diagnosis of the primary cause should always be aimed at for successful treatment. The indiscriminate use of anti-cough remedies may mask the true cause of the malady, which if early detected would have yielded a better result from the treatment. The treatment is both medical and surgical. The enlarged tonsils, uvula and adenoids should be removed under strict surgical asepsis. In pharyngitis secondary to dyspeptic conditions a correction of diet and avoidance of alcohol and tobacco in excess will do much more than the ordinary cough mixture. Rest in the recumbent position, fresh air, restriction of exercise and avoidance of fatigue should form the fundamentals of treatment. Warming of the bed in cold weather is of particular value in children. In the acute catarrhal stage, diet should always be liquid and warm feeds are better tolerated. Milk, barley, fruit juices and foods rich in vitamin A should be given. Heavy meals should

never be allowed to patients with chronic cough as these add to the distress of the patient during attacks of coughing.

Drugs. In selecting and prescribing proper expectorant drugs, the stage of the disease should be recognised. The drugs are classified as sedatives, stimulants and anodynes. The sedatives are useful in the acute inflammatory stage of the disease while the anodynes are of particular value in incessant cough which is ameliorated by the drugs. Sulphate of codeine ($\frac{1}{4}$ gr.) allays irritable cough from reflex causes. In combination with sedative expectorants, it is useful in excessive dry cough. Ammonium salts such as the chlorides and the carbonates increase the secretion of bronchial mucus. Terpene hydrate (3 to 5 gr.) lessens cough associated with excessive secretion. Tincture of belladonna and sulphate of atropine are useful drugs in whooping cough. Iodide of potassium (5 to 15 gr.), though a useful expectorant, should be prescribed with caution; bromides lessen the cough-reflex and are useful in whooping cough and hysteric cough. As cough is generally a manifestation of some constitutional disease, measures to promote general health should also be resorted to. Sometimes surgical measures to eradicate septic foci such as the removal of septic tonsils, or adenoid growths are of benefit. The following mixture is useful to lessen the congestion of the inflamed mucosa in laryngitis and tracheitis. Bicarbonate of sodium 15 gr., tincture of ipecacuanha 8 min., syrups of tolu and squill each $\frac{1}{2}$ dr., spirit of chloroform 10 min., and infusion of senega to 1 oz., one dose every four hours until the expectoration is free. In these cases compound tincture of benzoin a drachm to a pint of boiling water, to which 3 min. each of menthol and oil of eucalyptus have been added, serves as a useful inhalation. Warm olive oil applied round the neck may relieve the cough of laryngitis and tracheitis. The following mixture is useful in the early stages of bronchitis when the cough is painful and non-productive. Wine of antimony 15 min., chloride of ammonia 10 gr., spirit of chloroform 10 min., syrup of orange 40 min., camphor water to 1 ounce. The mixture should be discontinued as soon as the sputum becomes free. The following alternative mixtures are helpful in the later stages of bronchitis when expectoration is copious. (1) Carbonate of ammonia 5 gr., tincture of nux vomica 8 min., tincture of squill 15 min., and water to 1 oz. (2) Carbonate of ammonia 5 gr., tincture of squill 15 min., compound tincture of opium and camphor 20 min., and infusion of senega to 1 oz. The above mixtures are of the stimulating expectorant type. The following mixture is useful for children suffering from cough and where the expectoration is just beginning. Tincture of ipecacuanha 2 min., compound tincture of opium and camphor 5 min., nitrate of potassium 2 gr., honey 30 min., and water to 2 dr. The sedative drugs prescribed for the dry cough preventing sleep in tuberculosis cases are: (1) Heroin $\frac{1}{12}$ gr., syrups of virginian prunes and of codeine, each 30 min., and water to $\frac{1}{2}$ oz. (2) Heroin $\frac{1}{12}$

gr., codeine $\frac{1}{8}$ gr., dilute sulphuric acid 2 min., glycerine 10 min., syrup of tolu 1 dr. For these cases the useful drugs for inhalation include menthol 40 gr., creosote 40 min., rectified spirit $\frac{1}{2}$ oz.; a few drops of this to be sprinkled on a mask and inhaled for a few minutes. Drugs such as chloride of ammonia and antimony are helpful in loosening the sputum. Cardiac tonics such as digitalis, nux vomica etc., relieve the cough in fibrosis of the lungs associated with dyspnoea caused by failure of the right ventricle of the heart. The following is a useful combination: (1) Tincture of digitalis 5 min., carbonate of ammonia 5 gr., tincture nux vomica 5 min., spirit of chloroform 10 min., and water to 1 oz. Belladonna is invaluable in coughs where an antispasmodic effect is desired. The following is a useful prescription: Tincture of sumbul 15 min., tincture of stramonii 10 min., tincture of belladonna 5 min., spirit of chloroform 15 min., water to $\frac{1}{2}$ oz.

Useful local applications to the throat including the tonsils are: (1) Iodine 5 gr., iodide of potassium 10 gr., liquid carbolic acid 3 min., glycerine up to 1 oz. (2) Resorcin 40 gr., spirit of peppermint 5 min., glycerine up to 1 oz. These are useful for chronic pharyngitis. The paints are to be applied morning and evening daily with a sterile cotton wool swab.

Inhalations. Menthol $\frac{1}{2}$ dr., camphor $\frac{1}{2}$ dr., compound tincture of benzoin up to $1\frac{1}{2}$ oz. A teaspoonful of this mixture is added to a pint of hot steaming water and the vapour arising out of this is inhaled by the patient. A few drops of compound tincture of benzoin only may be added to hot water and the vapour inhaled. The drugs lubricate the respiratory passages and facilitate expectoration.

Sprays. Camphor 4 gr., oil of eucalyptus and peppermint, each 4 dr., paroline up to 4 oz. The mixture is used in a DeVilbiss spray for the nose and throat.

CRAMPS. These are painful spasms of the voluntary muscles resulting in temporary loss of function of the part affected. In most cases it is suggested that the condition is due to a deficient supply of blood which is not in keeping with the amount of work performed by the affected muscle. Such an explanation is applicable to cases such as intermittent claudication or angina cruris, where a spasm of the vessel wall precedes the cramps. The group of muscles affected presents signs of exhaustion and various factors are held to predispose to it. Overwork, cold, unfavourable environment, etc., are a few of the many predisposing causes. Compression of nerves is held to be an exciting cause in cases of cramp such as follows from sitting on the hard, sharp edge of a chair, badly fitting splints and the use of crutches. A very painful form, affecting often the abdominal muscles and lasting for a prolonged period is met with in individuals working in foundries amidst high temperature. In cases where body fluid is enormously drained out as in cholera and severe diarrhoeas, cramps are attributed to defective

circulation consequent upon the enhanced viscosity of the blood. Other common causes of cramp include chronic gout, chronic interstitial nephritis, anaemia, Raynaud's diseases, tetany, tetanus, strychnine poisoning, ergotism and the paraplegias. Cramp is very often met with in occupational neuroses where there is a disturbance of motor function and is particularly seen when some movements are attempted by individuals in the course of their occupations. It is generally associated with neurasthenia though actual neuritis, arterio-sclerosis of the vasa vasorum, etc., are met with in many cases which distinguish them from idiopathic occupation neuroses. The common forms are those of writers, telegraphists, violinists, typists, pianists, cigarette-markers, etc. It is also seen in the leg muscles of turners and lathe-workers, and in the face muscles of players on wind instruments, glass blowers, etc.

TREATMENT. The treatment of cases should aim at treating the primary causes. Rest, hot applications and baths, suitable massage and exercises are effective measures in the treatment. Antipyrin 10 gr., on retiring is often efficacious in troublesome cases. In occupational neuroses prolonged rest of the part is imperative and later on new methods of carrying on such occupations should be cultivated. Drugs are of little value in these cases and local treatment to the fore-arm and hand is often effective. Electrotherapy in the form of galvanic baths or galvano-faradism is often recommended. Hydrotherapy and other general measures should be adopted in neurasthenic cases. Saline infusion is of particular value in all cases of cramps and has been very lately advocated.

DEAFNESS. Of the various factors contributing to the causation of deafness, a large variety of pathological conditions, infective or bacterial in origin, grouped under 'chronic catarrh of the middle ear' is considered to be the most important one. Pathologically the changes include subacute or chronic sero-mucous inflammation of the mucosa of the Eustachian tube and middle ear. The resulting deafness is obstructive and progressive in type. The common causes leading to chronic catarrh of the middle ear are acute and chronic hypertrophic catarrhs of the nose and throat, adenoids, septic tonsils, infectious diseases such as measles, scarlet fever, diphtheria, etc. The condition often recurs and ultimately results in atrophy or in the development of adhesions within the tympanum. The chronic atrophic catarrh of the middle ear is generally ascribed to depressing conditions such as rheumatism, gout, cold, alcoholism and Bright's disease. Sometimes these middle ear changes in adults may be the after-effects of slight acute or subacute catarrhs in infancy and early childhood. Others hold the changes to be due to constitutional toxic processes or these may be secondary to bacterial infection in the sphenoidal and other nasal accessory sinuses. The prominent symptoms are tinnitus and progressive deafness. The tinnitus is continuous and persistent and varies in quality from time

to time. The deafness is obstructive in type and tends to get worse as time advances in defiance of treatment. The younger the patient is when the disease sets in, the more likely it is to end quickly in grave loss of hearing. The tympanic membrane in middle ear deafness is usually retracted, dull, lustreless, opaque and thickened. A similar clinical condition known as otosclerosis, or an ankylosis of the stapedia-vestibular articulation, is also an important cause of deafness. It is commonly known as ear-hardening and the ætiology is obscure. Tinnitus is the most distressing symptom in this condition and it is continuous and high pitched. Chronic middle ear diseases and otosclerosis often affect the internal ear resulting in lesions of the cochlea. Nerve deafness is very often associated with former conditions mentioned and in conjunction with the signs of nerve deafness, signs and symptoms of vestibular involvement are often met with. A long continued painful noise may be followed by deafness and nerve deafness results from prolonged exposure to noise in the course of an individual's occupation. This type of deafness seems to be due to the injurious action of the intense stimulus upon the organ of Corti as signs of degeneration are met with in it. This is an occupational disease met with among individuals working in the navy, artillery, boiler-making, etc. Other causes of deafness are fracture of the base of the skull, syphilis particularly during the secondary stage of the disease and also in the congenital type, epidemic cerebrospinal meningitis, mumps, typhoid fever, myxœdema, old age (senile deafness or presbycusis), drugs such as quinine, salicylates, arsenicals, etc., shell-shock, hysteria and neurasthenia.

TREATMENT. In treating middle ear deafness the primary causes should be treated first. The lesions of the nose and naso-pharynx should be promptly attended to. Adenoids and tonsils if pathological, should be removed, deflected nasal septa rectified, hypertrophied turbinates removed and suppurating nasal sinuses laid open for free drainage. Locally, the ears should be inflated every two or three days with Politzer's bag as this keeps the Eustachian tubes patent and aids in the expulsion of the retained tympanic exudate. After the acute stage has subsided, Eustachian catheterisation may be resorted to and vapourised iodine and camphor at a fairly high temperature may be passed into the tympanum through the catheter. In cold damp weather, the patient should keep himself warm indoors in an equable temperature. The patients' habits and mode of life should be regulated, unfavourable occupations changed and local irritants, such as tobacco and alcohol, should be avoided. Deafness due to fibroid changes in the middle ear and otosclerosis is difficult to cure. The distressing symptom of tinnitus can to some extent be relieved by ionization with silicon and calcium and by administration of parathyroid gland. Administration of iodide of potassium in moderate doses over prolonged periods is said to be an effective therapeutic measure in otosclerosis. Intestinal stasis should be treated on usual lines and iron administered

internally in those cases associated with anæmia, is said to yield hopeful results. Local treatment by catheter and by inflation is of no avail in genuine otosclerosis. The essential treatment in these cases is to re-educate the dormant centre of hearing and the best re-education medium is the human voice. This is carried out by means of a binaural speaking tube into which the patient reads aloud or is spoken to for a ten-minutes' sitting, three times a day. The more intelligent the patient is, the more rapid is the recovery of this power. Deafness is incurable in cases of true degeneration of the auditory nerve. In noise deafness people should plug the meatus with some material relatively impermeable to sound. This gives a partial protection as the sound can even then reach the cochlea through the bones of the body and head. In all cases people sensitive to noise should plug the ears when exposed to it. Concussion deafness and that arising from fracture of the base of the skull are irremediable. In syphilitic deafness, anti-syphilitic remedies, especially mercury and iodide of potassium, are of definite value. Politzer recommends hypodermic injections of a 2 per cent. solution of pilocarpine nitrate for eight to fourteen days in these cases. Pritchard reports great benefit from blistering the mastoid processes in congenital syphilitic deafness.

Prevention. On a review of the ætiology of deafness, it is noticed that, with the exception of congenital deaf-mutism and otosclerosis, it is an acquired condition. The problem of prevention resolves itself mainly into an early detection and correction of predisposing factors. Improper dieting, malnutrition, exposure to damp and cold tell upon the health of the growing child. The presence of adenoids and the germ-choked tonsils subject him to frequent colds and sore-throats and the Eustachian tube is subject to frequent and recurrent inflammations. The exanthemata, whooping cough, influenza, diphtheria and broncho-pneumonia are the most frequent causes in childhood. It is during the course of one of these fevers that the trouble generally arises in the middle ear. If the labyrinth is involved the hearing is completely destroyed. On the other hand, if the inflammation localises itself to the middle ear, a chronic otitis media results. As there is always a tendency for relapse in the catarrhal type of inflammation, children should be watched during the acute attacks of inflammation and measures adopted to bring about a complete resolution. In acute otitis media, myringotomy should not be delayed if the pain is very severe, and the usual conservative treatment affords no immediate relief. Persistent discharge from the ear, and deficient hearing are the most common and obvious indications for the removal of adenoids and tonsils. Nasal accessory-sinus diseases are not uncommon in children and should receive attention. Body resistance must be built up, dietetic errors must be corrected, and the general health improved. Further prophylactic measures lie in educating the general public and the

educational authorities. Preference must be given to hearing tests rather than disciplinary measures at school.

DENGUE. See page 987.

DIABETES. See page 1043.

DIARRHŒA. It is a very common complaint in the tropics. It should be regarded as a symptom, not as a separate disease. The general causes of diarrhœa include all factors which increase the fluid content of the fæces. It may be produced by (a) rapid passage of intestinal contents through the large intestine before the absorption of the fluid has been completed, or (b) by an excessive secretion of the lining membrane of the intestinal tract, or (c) both factors combined, because generally what causes increased peristalsis also stimulates secretion.

The individual causes of diarrhœa are:—(1) Dietetic errors. Ingestion of large quantities of food or fluid may produce diarrhœa from the (i) stimulus due to bulk, (ii) increase of fluid content of the gut, (iii) defective digestion, (iv) excessive fermentation, and (v) irritation.

The inhabitants of the tropics, especially the new-comers, are especially liable to this type of indisposition. Their digestive organs, especially the liver, are continually over-stimulated, producing *tropical liver*, which is characterized by attacks of hepatic congestion and hepatitis. Unsuitable food is a very frequent cause of diarrhœa in children. Milk is often a source of illness, as its supply is not always satisfactory. Too much over-ripe fruit or rich foods cause intestinal disturbance. (2) Specific organisms—dysentery organisms are frequently associated with tropical diarrhœas. The attacks usually alternate between dysentery relapses. Alternate constipation and diarrhœa is a common manifestation of chronic amœbiasis. Chronic Flexner infection often gives rise to protracted diarrhœa. *Bact. pseudocarinatus*, a mutated Flexner type (phage modified), is another cause, organisms of the Morgan group also cause severe diarrhœa; *Ps. pyocyaneus*, *Bact. faecalis alkaligenes* and *B. proteus* and certain types of streptococci may produce similar symptoms.

Outbreaks of diarrhœa due to food poisoning are not uncommon; tinned meats and rotten flesh or fish cause diarrhœa, Gærtner's bacillus being the organism commonly found. Certain helminths, especially schistosomidæ, cause intestinal irritation and diarrhœa. (3) Chemicals or mechanical irritants, e.g., salts arsenic, arsenic, certain waters (they contain salts and suspended particles of clay, mica, vegetable debris or some organic matter). (4) Diarrhœa associated with other diseases, e.g., intestinal disturbances are common in typhoid, undulant fever, kala-azar, relapsing fever and malaria; tuberculosis of the intestines and malignancy of the rectum cause diarrhœa. (5) Diarrhœa of unknown causation, e.g., sprue and hill diarrhœa, are tropical affections of this nature. See page 879.

Predisposing factors. Insanitary surroundings, over-crowding as in large cities, exposure to chill, prevalence of flies, etc., are important predisposing factors; low-lying, damp and badly drained places contribute to the disease. Such conditions together with high temperature, humidity and rainfall are favourable to the production of diarrhœa in endemic form. The morbid appearances depend upon the cause, the severity and the position of the irritative process. There may be (i) no visible lesion or (ii) only simple congestion of the lining layer, or (iii) actual ulceration may be present. In chronic cases the intestinal wall becomes thin and atrophic and the patient becomes emaciated and anæmic.

Symptoms depend on the cause of irritation and the part of the bowel involved. If the upper part of the small intestine only is affected the diarrhœa is not so watery but motions contain undigested food. If the large intestine is affected there is excessive mucus. The stools are greenish when bile is passed out unaltered. They are pale or white if diarrhœa is due to derangement of the liver. If there is excessive fermentation with gas formation stools become frothy and acid. There is inflammation about the anus if the stools are very irritating. In acute cases, fever, vomiting and pain in the abdomen may be troublesome; the patient becomes prostrated from dehydration and toxæmia. Asthenia, anæmia, emaciation, œdema of the feet, purpuric spots are met with in chronic cases.

DIAGNOSIS. It depends on the cause. (1) Repeated examinations of stools, macroscopic, microscopic and bacteriological, are very important. (2) Blood examinations especially in the early stages are advisable. (3) Agglutination of the blood against dysentery bacilli may be positive. (4) Wasserman's reaction if syphilis is suspected. (5) Rectal examination (ulcer, stricture, new growth) should never be missed in a chronic case. (6) Sigmoidoscopy should be done. (7) Barium meal and barium enema may give very useful information.

TREATMENT. (1) Rest in bed if the attack is severe. (2) Diet. No food for the first 12 hours; afterwards give albumin water, barley water, rice water (4 oz. every 2 hours); later milk, arrowroot, sago, and rice may be given. As recovery takes place give fish and eggs; meat and vegetables should be withheld until all traces of irritation have disappeared. In infants, if breast-fed and the milk is well digested, no change is necessary. If bottle-fed or if curds are found in stools, stop milk, keep on water for 24 hours, then give whey, 3 per cent. lactose or 10 per cent. dextrose solution. If there is too much fermentation give Bulgarian sour milk. In chronic cases give raw meat juice in teaspoonful doses; preparations of dried milk may be tried. (3) Drugs. (i) A preliminary purge, viz., castor oil or fractional doses of calomel followed by salts are helpful in early stages; (ii) later bismuth salicylas 10 gr. with Dover's powder 5 gr. or chalk mixture, or osmokaolin may be given to control the diarrhœa and allay pain. (iii) If motions are

acid and irritating apply alkalis and olive oil locally. (iv) For fermentation give salol 5 to 10 gr. or beta-naphthal 2 to 5 gr. (v) For indigestion add pepsin 10 gr. (vi) For vomiting, gastric lavage is useful. (vii) For collapse, warmth, stimulants and saline, preferably hypertonic, should be given. (viii) If diarrhœa is found to be due to a specific cause, treat accordingly.

Prophylaxis. (1) Food should be fresh and well cooked and without any irritants. (2) Milk and water should be pure. (3) Overfeeding and excesses are to be avoided. (4) Regular action of bowels and exercises are important. (5) Avoid chill and exposure to the sun. (6) Supervision of kitchen and servants is essential.

DIETS AND DIETETICS. See page 146.

DIET IN DIARRHŒA. In acute diarrhœa nothing but plain water or barley water is given for a day or so. When the symptoms have somewhat abated, weak decoctions of cereal preparations, *viz.*, arrowroot, sago, *chitra* are given. Milk is gradually added and then other non-irritating preparations.

In cases of chronic diarrhœa diet depends on the cause. If it is due to carbohydrate fermentation (acid stools) milk, casein preparations, soup, fish and meat (specially underdone) suit best. If, on the other hand, there is protein decomposition (alkaline offensive stools) the diet should consist of carbohydrates. If the stools are white, greasy and show fat droplets, fat should be withheld from the diet.

DIET IN DYSENTERY. Diet in infections with *B. Flexner*. For *Europeans*. Albumin water, whey, milk (citratd or uncitratd), starch-free prepared milk food like Allenbury's No. 1, Glaxo, etc., soup, boiled fish, lightly boiled or poached eggs, minced chicken, *Vita weat* biscuit, etc. For *Indians*. Indians depend mainly on milk preparations, such as whey, butter-milk, *dahi* and *chhana*. Whole milk (citratd or uncitratd), starch-free prepared milk food, albumin water, lean fish (boiled and flavoured with coriander, cloves and salt). Any article recommended for Europeans may be used by those Indians who prefer a meat diet.

Articles of diet commonly used but contra-indicated. Barley, arrowroot, sago, rice and sugar. Ordinary biscuits and bread are also unsuitable.

DIET IN INFECTIONS WITH B. SHIGA, B. STRONG, AND IN CHOLERA. Starchy protein-free diet, such as barley water, arrowroot water, sago and glucose water.

DIET IN TYPHOID FEVER. In the acute stage $1\frac{1}{2}$ seers of milk is given daily, diluted with barley water or lime water in measured quantities at 2 or 3 hourly intervals. The nutrition value is increased by the addition of glucose, lactose, plasmon, cream, Horlick's, etc., to the milk. Tea and coffee may be allowed in moderation and the monotony of the diet varied by the addition of soup, broths and orange juice.

Plenty of cold plain water is given in between the feeds. Should intestinal discomfort occur or curds appear in the stools milk is citrated or peptonized. Milk is substituted by whey and albumin water if there is much diarrhoea or tympanitis. Such things as lightly cooked eggs, custards, bread-crumbs and milk, etc., may be given, if liked by the patient, in the absence of much toxæmia and complications.

DIET IN CHRONIC INTESTINAL STASIS. A bulky diet that leaves a large amount of residue is recommended. It includes oatmeal, green vegetables, wholemeal bread, fruits (especially prunes, figs, apples, bael), etc. Fats and oils are also increased in the diet. A glass of cold water should be taken early in the morning on rising.

MODIFIED SIPPY DIET The aim is to keep the stomach free from active hydrochloric acid. This is accomplished by giving a quantity of fat in the form of cream and olive oil, big doses of alkalies after and atropine before the feeds. Three ounces of a mixture of milk and cream, which may be citrated, are given every hour from 7 a.m. to 7 p.m. Eggs are added after two or three days, first in the form of egg-flip and later, lightly boiled. Well cooked farinaceous foods are gradually included in the diet after the pain has subsided. The amount given in each feed should not exceed 6 oz. Half an hour after each feed a powder containing sodium bicarbonate 10 gr, heavy magnesia 10 gr., is given alternately with a powder of bismuth carbonate 10 gr., sodium bicarbonate 10 gr. Half an ounce of olive oil is given immediately before alternate feeds, and atropine 1/100 gr., or tincture belladonna 5 min., immediately before the other feeds. The amounts of magnesia and bismuth may be so regulated that neither constipation nor diarrhoea results. Double and triple carbonate powders may be used alternately for this purpose, calcium carbonate being preferred to sodium bicarbonate as the former does not produce an increased secretion of acid in the stomach.

The after-treatment of gastric and duodenal ulceration is important, and certain guiding principles can be laid down.

1. Regular habits should be formed; meals should be small and the interval between them short (not more than 3 hours).

2. The teeth should be put in order and regular visits paid to the dentist. Food should be taken slowly and be well masticated.

3. The bulk of fluid should be taken between meals.

4. Take especially eggs, milk, custards, jellies, cereals, vegetables, bread, butter, cream, soft puddings, fish and biscuits. Take meat once a day, in small amounts, but avoid tough meat, high game, bacon and pork. A little light wine may be taken with food; salt should not be taken in excess. Smoke only in moderation and not before meals. Take the powders thrice daily and once in the night if awake.

5. Avoid highly seasoned food, cooked cheese, lemon juice, marmalade, pickles, spices; vinegar, acid fruits, strong tea, coffee or cocoa;

rough foods, very hot food, especially meat soups and any alcohol on an empty stomach. Starchy articles of diet that have been cooked in fat, *e.g.*, fried potatoes and fried bread, should be avoided.

6. Regular action of the bowels is essential.

KETOGENIC DIET. It has very recently been introduced in medicine as a therapeutic measure in many diseases. It has been used with favourable results in chronic urinary infections, epilepsy, and migraine. The presence of ketone bodies in the urine has an inhibitory action on bacterial growth. The ketogenic diet contains a preponderance of fats over carbohydrates and proteins. When it is necessary to continue this dietary régime for a long time it is of paramount importance that the patient should receive an adequate amount of protein, vitamins and minerals in order to avoid a dietary deficiency syndrome. The proportion of fat to carbohydrate and protein combined is 2 to 1 or even 3 to 1. Such a diet may contain 40 gm. carbohydrate, 50 gm. protein and 180 to 250 gm. fat. The object is to produce a urine, the pH of which is between 5.1 and 4.9. If the diet produces nausea or otherwise disagrees with the patient, a small amount of orange juice and a short period of fasting will usually relieve these symptoms.

The effective bacteriostatic factor in the urine of patients on ketogenic diet is β -hydroxybutyric acid. Puller has also shown that aceto-acetic acid and acetone have slight bacteriostatic power. Mandelic acid, a hydroxy-acid, is excreted completely unchanged in urine after oral administration and has been used in recent years to replace the ketogenic diet. The routine method adopted has been to give 12 gm. of mandelic acid daily in divided doses whilst the fluid intake is limited to 2 pints. As with ketogenic diet the urinary pH should be controlled.

INVALID FOOD PREPARATION. (1) *Barley water.* Take 2 oz. of pearl barley and wash it well with cold water. Put it up in a saucepan with 1½ pint of water and simmer for about half an hour. Strain, sweeten with sugar and a few drops of lemon juice and serve.

(2) *'Chira' gruel.* A tablespoonful of fresh *chira* (pounded rice), well washed with cold water is made to simmer in a saucepan with a pint of water for 15 to 20 minutes and then strained. It is now flavoured and served.

(3) *Rice gruel.* A tablespoonful of fine and well-seasoned old rice is first washed with water and then boiled in a saucepan with one pint of water for ¾ to 1 hour. This is strained and the gruel so formed is served properly flavoured. This is very suitable for convalescent typhoid patients, preliminary to solid food.

(4) *'Sooji' gruel.* One tablespoonful of *sooji* is added to ¼ to 1 pint of water and is made to simmer in a saucepan till made into a rather thick gruel. It is now served with sugar.

(5) *Lime whey.* Boil ½ pint of milk in a saucepan. When it is bubbling, add sour lime juice drop by drop till the milk curdles. Strain to separate the curds and the light green transparent fluid is the whey.

It should not have a milky appearance and it should not be made too sour.

(6) *Sherry whey*. Boil $\frac{1}{2}$ pint of milk in a saucepan, and 2 oz. of sherry and strain.

(7) *Powdered milk food*. *Plain milk powder* (Lactogen, Glaxo, Allenbury No. 1) or the same mixed with malt (Nestle's, Horlick's, Allenbury No. 2, Milk food), is prepared by first making a paste of the powder with cold water and then slowly adding hot water and thoroughly mixing with a spoon. The quantity of the powder required depends on the thickness of the preparation desired.

(8) *Powdered food, prepared with milk*. Mellin's food (malted carbohydrate). Allenbury's malted food (mixture of wheat flour and malt) or Sanatogen (containing casein glycono-phosphate) is prepared by making a paste of the powder with cold water and then slowly adding hot milk. One or two teaspoonfuls are usually required for a cup of hot milk. Ovaltine (a special variety of cocoa containing malt and milk powder) and Vitavose (containing vitamin B, maltose and dextrin) are also prepared in the same way.

(9) *Peptonising milk*. To $\frac{3}{4}$ pint of boiled cold milk, add $\frac{1}{2}$ pint water and heat the mixture to about 140°F. (just hot enough to be bearable on the skin). Into a saucepan, put either two teaspoonfuls of liquor pancreaticus and $\frac{1}{4}$ a level teaspoonful of sodium bicarbonate or one tube of peptonising powder and make into a paste with cold water. To this the warm milk is now slowly added and thoroughly mixed. This is kept covered in a warm place or in a water-bath for about 10 minutes. The preparation is again brought to boiling point to stop further action of the ferment as overaction makes the preparation bitter. It is now sweetened and served. Milk is often peptonised with Benger's food (containing a mixture of wheat flour and pancreatic extract).

(10) *Junket*. Take lukewarm milk, add sugar to it, put into a deep enamel dish and add essence of rennet or rennet powder in quantity indicated on the label. Keep it undisturbed in a warm place or on a water-bath for 1 to 1 $\frac{1}{2}$ hours, when it sets. Serve with sugar. It is an easily digestible and palatable convalescent milk food.

(11) *'Dahi.'* May be prepared in the same way as above. Instead of rennet, a teaspoonful of good *dahi* from the bazar is added to a pint of luke-warm milk and put in a warm water-bath till it sets which usually takes 1 $\frac{1}{2}$ to 2 hours. This should be taken before it turns acid.

(12) *Oatmeal porridge*. Two tablespoonfuls of oatmeal and a pinch of salt are added to one pint of boiling water and slowly cooked, stirring briskly. This is continued for 20 to 30 minutes till it is sufficiently thick. It may be cooked with milk and sugar or these may be added afterwards.

(13) *'Sooji' porridge*. It is prepared in much the same way, milk and sugar being added when the *sooji* is partly boiled, the whole thing being then brought to a semi-solid consistency.

(14) *Typhoid bread*. Take the inside soft pulp of the bread and put it into boiling milk. Make the whole thing into a paste by rubbing down with the back of a spoon. This is strained and sweetened with sugar.

(15) *Albumin water*. Pour into a cup the white of a fresh egg and beat it thoroughly with a spoon and then slowly add water to make it up to 4 oz., and serve adding a pinch of salt and a few drops of flavouring.

(16) *Egg flip*. Beat 1 to 2 fresh eggs in a cup and then slowly add 8 oz. of warm milk and 1 to 2 teaspoonfuls of brandy. Sweeten as required.

(17) *Custard*. Beat up 2 eggs, add $\frac{1}{2}$ pint of milk, sweeten and flavour to taste. The preparation is now baked in a pie dish or steamed in a basin.

(18) *Patent meat-extracts*. Bovril (beef extract) and finely powdered beef fibrin, Brand's meat essences, Valentine's meat juice, Panopepton (beef extract with wheat) are sometimes substituted for fresh meat extracts. These are prepared by adding $\frac{1}{2}$ to 1 oz. of the extract to a teacupful of lukewarm water, if necessary flavoured with a few drops of lemon juice. These do not keep well in hot climates specially when the container is kept open for a few days. Once a tin is opened it should be used up. Virol, Roboleine and Marrow Malt are preparations of bone marrow with calcium, egg and malt.

(19) *Raw meat juice*. Finely mince $\frac{1}{2}$ lb. of lean mutton, put it in a saucepan and add 4 oz. of clean cold water. Allow it to stand in a cool place for an hour and then press the juice out either with a pressing machine or by squeezing through a clean piece of fine linen. One or two ounces of it are to be taken, flavoured with a few drops of lemon juice and a little pepper and salt.

(20) *Raw liver juice*. Prepared in the same way as raw meat juice and served fresh, or a cut piece of liver is taken and gently scraped with a dinner knife. The scrapings are collected in a tea cup, flavoured with orange juice and served.

DIPHTHERIA. DIAGNOSIS. Acute inflammation of the throat with definite membranous exudate, discharge from the nose, especially if unilateral and blood-stained, croup, cervical glandular enlargement, moderate pyrexia and the presence at times of albuminuria are important diagnostic points. Diagnosis should be aided by the bacteriological examination, but the bacteriological report does not exclude the disease if no Klebs-Löffler bacilli (*Corynebacterium diphtheriæ*) are found, and clinical cases should be treated as diphtheria without awaiting bacteriological confirmation.

TREATMENT. *Anti-diphtheritic serum.* To obtain the most successful results, anti-diphtheritic serum should be administered as early as possible (see page 799).

Local treatment. Local applications are of minor importance and if resisted by children it is advisable not to force this treatment and thereby exhaust the patient. In adults a spray of antiserum or the following lotion and hydrogen peroxide gargle will be found useful:—Sodium biborate, sodium bicarbonate, potassium chlorate, sodium chloride—each 7 gr., compound tincture of lavender $\frac{1}{2}$ dr. and water to 1 oz.

General. Absolute rest in bed is of great importance. In mild cases one pillow can be given, but in moderately severe cases the patient should rest without a pillow; in the most severe, not only should the pillow be removed but the foot of the bed should be raised a few inches (not more than 6 inches) to assist the flow of blood to the vital centres in the brain. As the circulation improves the patient should gradually be allowed to assume the normal recumbent position, then given an extra pillow, then allowed to sit up and lastly to get out of bed. He must be kept in bed for 4 to 8 weeks. *Diet.* Fluid diet (milk, barley, glucose, fruit juice, etc.) should be given during the febrile period. If there is difficulty in swallowing, thick Bengers' preparation may be tried. Bowels are best regulated by glycerine enema or mild aperients.

Treatment of complications. (1) For cough give glycerine or honey to sip or compound tincture of camphor, oxymel scillæ each 20 min., mucilage of acacia and syrup, each 1 dr. (2) For the laryngeal type give steam inhalation, atropine injection 1/200 gr. Tracheotomy or intubation is necessary if there is obstructed breathing as shown by increasing restlessness, dyspnoea, suction of the chest wall and cyanosis. (3) Circulatory failure in diphtheria. Diphtheria is attended with a profound toxæmia. The circulatory system is profoundly affected in diphtheria and from the commencement of the disease, a progressive fall in blood pressure is marked. Death takes place during the first ten days from circulatory failure. The general measures in treatment include absolute rest, and under no circumstances should the patient be allowed to sit up. He should be given an enema at regular intervals. Diet should comprise during the first week a bland fluid, beef extract, chicken broth, Benger's food. In all severe cardiac cases a nutrient enema is most beneficial. As the blood pressure attains normal level the patient may be allowed to recline in bed and be given a liberal dietary. Patients should always be kept warm and quiet with elimination of disturbing elements.

Many drugs have been tried but no specific drugs are known. Adrenalin is considered to be an efficient cardiac stimulant but owing to its rapid and transient action, ephedrine is much more preferred in these cases for its prolonged action. Antitoxin therapy can be safely

carried out after a preliminary dose of ephedrine. Ephedrine may be repeated every six hours but the drug does little good in moribund cases. The author has tried a tincture prepared from Indian species of *Ephedra* containing both ephedrine and pseudo-ephedrine with excellent results. In an extremely low condition of the patient, ephedrine may be combined with a maximum dose of pitressin, the blood-pressure-raising element of pituitary, and it should be given at six hourly intervals till the condition improves. The effect of the pituitary extract is absolutely specific in cases of circulatory failure in diphtheria. If the patient approaches an acute cardiac failure, intramuscular injections of pituitary and camphor in oil, which seem to aid the action of the heart, with the foot end of the bed raised, the patient kept very warm and a light linseed meal poultice applied over to cardiac region, are most helpful to tide over the crisis. If the patient is not vomiting a mixture containing spirit of ether, spirit of chloroform, aromatic spirit of ammonia in equal parts; one tea spoonful being given in a little water every four hours is most useful.

Other stimulants such as strychnine, digitalis and atropine appear to be of little use. Oxygen therapy is very useful in cases of cyanosis. All severe cases should receive brandy or alcohol, in some form or other and in maximum nutritional doses. In case of children it is usually administered as white wine which, if carefully prepared, is easily taken. The circulatory failure in diphtheria is due to vasodilatation, weakened cardiac output from the action of the toxin on the heart muscle and damage to the arterial wall, and provided that the antitoxin be given early enough, the blood pressure would not fall sufficiently to cause any serious circulatory failure; but should the antitoxin be given late for any reason or should the blood pressure fall from any of the previously considered factors then the only really effective treatment is in giving the vaso-constrictors.

(4) If toxæmia is severe, intravenous injection of 20 gr. glucose in 40 c.cm. of normal saline with 10 units of insulin hypodermically is of value. An alkaline mixture should also be given. (5) If swelling of the neck is present warm fomentations and local ichthol application are helpful. (6) Serum sickness. Calamine lotion or bicarbonate of soda lotion may be applied locally to relieve itching. Adrenalin and pituitrin in doses of 0.2 c.cm. may be injected intramuscularly. Calcium may be given by mouth. The bowels should be opened well. (7) Paralysis. The affected parts should be rested and strychnine administered followed by massage. If there is regurgitation of food due to paralysis of the soft palate, the patient will have to be fed by a nasal tube. (8) If there is broncho-pneumonia, treat it in the usual way.

DRUNKENNESS. Alcoholic intoxication includes an impairment of the physical and mental faculties to such an extent as to render an individual unable to execute safely his or her occupation. The three

stages of intoxication are exhilaration, in-co-ordination and drowsiness. All kinds of alcoholic beverages produce intoxication when the alcohol content of the blood reaches 0.15 to 0.2 per cent. The medical examination of a person alleged to be intoxicated is undertaken for the purpose of diagnosing conditions which simulate drunkenness such as those arising from the use of drugs. The routine examination consists in an observation of the temperature which is lowered, the pulse which is rapid, full and bounding, the pupils, dilated and sluggish to ordinary light and contracted in a bright light and in alcoholic sleep and the tongue dry and white. The ordinary speech and gait are unimpaired if the faculties are not notably affected. The breath smells of alcohol if it has been taken lately. Examinations for testing the higher psychical functions of the brain should be undertaken, such as questioning the individual as to his whereabouts, etc. The person's manner and appearance should be noted, the individual being often insulting, garrulous or taciturn. Specific tests should be applied to determine the state of the mental faculties by asking him the day of the week or the date of the month. The lack of co-ordination should be observed while walking on a crooked line or following some person two or three yards ahead of him. He may also be asked to touch his nose or pick up a coin from the floor. Reading tests and handwriting tests are also useful and valuable aids. For treatment see page 1452.

DYSENTERY. Dysentery means passage of blood and mucus with stools, often associated with abdominal pain and tenesmus. It is a symptom complex rather than a disease itself. Different types of dysentery are :—I. *Protozoal*—(1) Amœbic dysentery. (2) Flagellate dysentery—*Giardia intestinalis*, *Trichomonas hominis* and *Chilomastix mesnili*. (3) Ciliate dysentery—*Balantidium coli*. (4) *Leishmania* dysentery. (5) Malarial dysentery.

II. *Bacterial*—produced by such organisms as Shiga, Flexner, Gærtner, Bact. Pseudocarinus, S. morgani, Pyocyaneus, etc.

III. *Helminthis*. Trematode infection (Schistosomiasis).

Besides these, the following conditions may simulate dysentery. Carcinoma of the rectum, intussusception, polypoid conditions, tuberculous ulceration, piles and fistulae, specific ulcers, poisons, etc.

There may be dysentery infections without any blood and mucus in the stools.

AMŒBIC DYSENTERY. See page 356.

BACILLARY DYSENTERY. There are two main types :

1. *Dysentery due to non-mannite fermenting bacilli of the Shiga-Krause type.* This infection gives rise to marked pyrexia and toxæmia. Stools are 16 or more in number in 24 hours with blood and mucus ; no faecal matter is seen. There may be severe diarrhoea and collapse simulating cholera. In acute gangrenous types with paralysis of the

gut there may be no stools. The Shiga bacilli produce intra- and extra-cellular toxins, and also poisonous pressor bases from animal proteins.

2. *Dysentery due to mannite fermenting bacilli of the Flexner-Strong group.* This infection gives rise to moderate fever and less toxæmia. Stools are less than 16 a day. They contain blood and mucus but may not be visible to the naked eye. The flexner bacilli produce only intracellular toxin and also produce indol from animal proteins and ferment carbohydrates (except lactose).

Character of stools of acute bacillary dysentery. (i) Alkaline reaction, (ii) little or no faecal matter, (iii) bright blood intimately mixed with mucus, (iv) *not offensive*.

Microscopically the following cellular elements are found. (i) Large macrophage cells, (ii) numerous polymorphonuclear leucocytes, (iii) scattered red corpuscles, (iv) numerous desquamated columnar epithelial cells.

N. B.—Specimen of fæces should be examined and cultured as soon as passed (within three hours).

Blood shows leucocytosis. The serum may agglutinate the dysentery bacilli after the tenth day of the disease. With Shiga strains agglutinating power 1 to 50 is usually accepted as evidence of specificity, but for Flexner strains a dilution of 1 to 150 is required.

Treatment of acute bacillary dysentery. See page 842.

Symptomatic treatment. (a) In collapse—intravenous saline, atropine, stimulants and warmth. (b) In severe purging—kaolin mixture as in cholera.

Investigation of chronic cases. (1) Repeated examinations of the stools, (2) agglutination of serum with dysentery bacilli, (3) sigmoidoscopy, and (4) barium enema.

TREATMENT. (1) A course of autovaccine injections with calcium lactate 10 gr. and parathyroid extract 1/10 gr. by mouth. (2) Diet is carefully regulated, carbohydrates are eliminated as far as possible and proteins are given, *viz.*, fish, chickens, eggs, etc. (3) A thorough overhaul of the digestive system is made. (4) Bacteriophage may be tried. It is particularly useful if the organism is lysable by the phage. If necessary bacteriophage can be grown on the causative organism and then administered to the patient. (5) Medicated enemas or bowel washes are sometimes very useful in healing chronic ulcers. (6) Symptomatic treatment.

ELECTROTHERAPY. See page 125.

ENURESIS. This is a fairly common complaint among children and in some the habit may even persist till adult life. Up to the age of a year, children generally exercise no control over the bladder during the waking hours and pass water during sleep till the age of 2 years. In some children full control of the bladder is never attained and the incontinence is referred to a previous accident or an illness. It is

usually during the first half of the night that the incontinence occurs and such trouble may be intermittent. The children are otherwise normal but often they exhibit neuropathic taints such as excitability, timidity or they may be deficient mentally. The habit is also met with in apathetic children with hypertrophied tonsils and adenoids. Of the other factors concerned three diseases in children are associated with the passage of an excessive amount of urine and these are diabetes mellitus and insipidus and chronic nephritis. Diabetes mellitus tends to be acute in children with the usual symptoms of wasting, thirst and polyuria. Diabetes insipidus is rare in children and when present there is copious output of urine of low specific gravity often associated with disordered hypothalamo-pituitary function. Syphilis is suggested to be a common cause in some. Chronic interstitial nephritis may be a congenital condition and in this enuresis may persist from childhood. Some congenital deformity of the urinary tract is also a causal factor. Congenital hypertrophy of the bladder in children may be due to phimosis, a pinhole urinary meatus, or the presence of valves in the posterior urethra obstructing the passage of urine. When these defects are absent, hypertrophy of the bladder is supposed to be due to a neuro-muscular incoordination between the sphincter and detrusor muscle of the bladder. So, as a rule, in every child brought for examination, the hypogastrium should be carefully palpated to exclude a functional cause. Routine examination of the urine should be undertaken in all cases; hyperacidity of the urine when present results in frequency of micturition rather than incontinence. Beside phimosis, other local causes such as the presence of threadworms, carious teeth, etc., should be borne in mind. The possibility of epilepsy should not be lost sight of. Intake of an excess of mustard and pepper has been found responsible for nocturnal incontinence.

Treatment. Before adopting any specific drug treatment, thorough investigation and subsequent correction of all local irritative processes should be undertaken. Worms should be expelled by proper anthelmintics, tonsils and adenoids should be removed under surgical asepsis and an operation of circumcision may be performed in cases where there is much retention of septic materials under a long and tight prepuce. The urine should be rendered alkaline with suitable alkalis where it is hyperacid. Of all the effective measures in controlling the habit, education of the child is thought to be the most important one. The child should be taught to evacuate the bladder at regular intervals particularly during the daytime. At night he should be made to pass water before going to bed and immediately on awakening in the morning. The time of bed wetting should be roughly determined beforehand and the child may be awakened at that hour to pass urine. Such a training should be imparted quite early in the life of the infant, and the child should never be reproached for the act. Punishment often makes the situation worse. With regard to psychotherapeutic

methods, simple suggestion acts best when the removal of the coexisting defects has failed to cure. The diet should be plain, simple and nourishing and free from indigestible coarse materials that are likely to cause irritation of the bowel. The amount of fluid intake should be restricted before the child is put to bed. Belladonna has had the reputation of being a specific in enuresis. The drug in combination with hyoscyamus and bromide may help for a time or even cure the condition. The usual advice is to push the dosage until the child is on the verge of physiological effects such as dryness of the throat. The initial dose suggested is 7 min. of the tincture given thrice daily and the dose should be increased by 2 min. every four or five days until as much as 30 or even 60 drops are being taken at each dose. When the bedwetting diminishes the dose of belladonna may be maintained for two or three weeks and then gradually reduced, the whole course covering a period of about three months. Ergot is similarly reputed to be a valuable drug in the treatment. A favourite prescription for a child of 5 years contains liquid extract of ergot 5 min., liquid extract of glycyrrhiza 2 min., flavoured with a drop of peppermint oil and given thrice daily for nearly a fortnight. Strychnine in the form of tincture of nux vomica is worth trying in combination with the previous drugs. Ephedrine hydrochloride in doses of $\frac{1}{4}$ to $\frac{1}{2}$ gr. has been found effective in cases of functional enuresis, the action of the drug being due to sympathetic stimulation. Deficient thyroid secretion is suggested as a cause of nocturnal enuresis and such children are obese, present cold extremities and are mentally backwards. Thyroid therapy has given encouraging results in some of the dull and apathetic children. In debilitated children the general health should be improved with tonics, suitable exercises and nourishing diet. Electrical therapy in the form of faradic or galvanic current, with one pole applied over the bladder and the other in the perineum is sometimes of service.

EPIDEMIC DROPSY. See page 1023

ERYSEPELAS. See page 1162.

FEVERS IN TROPICS (See page 202). Fever is one of the commonest symptoms for which patients come to a practitioner in the tropics. Investigation of a fever case is very important. To investigate such a case we should have: (A) *History*. The nature of onset, the type of the fever, the duration, etc., greatly help the diagnosis. But an accurate history is hardly obtainable especially from illiterate persons and often it is unreliable. When an accurate history is available, the evidence that fever has already lasted for so many days enables one to exclude at once the exanthemata, if a rash is present, however, it helps greatly to diagnose an eruptive fever. A history of previous similar attacks is also helpful (e.g., in malaria). As far as possible an endeavour should be made to take an accurate history of every febrile case. (B) *Clinical examination*.

This must be thorough and conducted systematically. The patient should be examined from head to foot. Attention should first be directed to any focus of localized infection. For this, particular attention must be paid to the patient's statements as to his chief complaint, his position, appearance and movements. Careful attention should be paid to: (1) Examination of the surface of the body for any rashes, adenitis, lymphangitis. (2) Examination of the throat for any inflammation, patch, etc. (3) Examination of the gums and teeth for pyorrhoea, caries or apical abscess. (4) Examination of the nose, ear and sinuses for any septic focus. (5) Examination of the lungs, which may present physical signs suggesting local infection. In this connection, however, it must be remembered that lung complications are quite common in certain general infections. For instance, friction sounds may be heard over the left lower ribs in connection with a rapid and painful enlargement of the spleen due to malaria. A certain amount of bronchitis is frequently present in enteric fever, undulant fever often causes bronchitis or broncho-pneumonia about the beginning of the third week. Hypostatic congestion is met with in many conditions. Pulmonary congestion and inflammation occur in typhus, plague, influenza, meningitis, hydatid disease of the lung, schistosomiasis and paragonimiasis. (6) Examination of the heart for any lesion, particularly endocarditis. (7) Examination of the abdomen for any disorder of the spleen, liver, gallbladder, appendix and colon. Rectal and vaginal examinations should be made whenever required. Prostatic and cervical smears are to be examined if there is suspicion of any infection. (8) Examination of the joints should be made when patients complain of fever with pain in the joints. They are not always of rheumatic origin. Rheumatic fever should not be diagnosed if only one joint is involved, or suppuration occurs, and the swelling does not subside in a few days (at most 15 days) and if there is no improvement with salicylates. Undulant fever also causes pain in the joints which become swollen, hot, tender and painful. Salicylates have no effect in such cases. Recovery of *Br. melitensis* from blood or urine and agglutination reaction will settle the diagnosis in such a case. Bacillary dysentery may give rise to polyarthritis. Arthritis due to dysentery should be distinguished from acute rheumatism by the mode of onset, lack of redness and heat in the joints, chronic nature, failure of response to salicylates, absence of endocarditis, and evidence of dysentery. Agglutination of the patient's serum against the dysentery group of bacilli may help the diagnosis. Gonorrhoeal arthritis is often monoarticular. Dengue and trench fever may cause much periarticular pain. Filariasis may cause synovitis. Besides, arthritis may complicate cerebro-spinal fever, typhoid, pneumonia, syphilis, yaws, amebiasis and any form of chronic sepsis.

If after a thorough physical examination one fails to detect evidence of localized infection, generalized infection should be suspected:

(1) Fever with gradual onset may be enteric fever, *Bact. coli* infection, liver abscess, undulant fever, kala-azar, syphilis, tuberculosis, bronchial spirochaetosis, etc. (2) Fevers of sudden onset are numerous, *viz.*, malaria, typhus, relapsing fever, trench fever, plague, small-pox, heat-stroke, meningitis, pneumonia, etc. (3) Hyperpyrexia may occur in malaria, heat-stroke, meningitis, cholera (reaction stage), yellow fever, scarlet fever, etc. (4) Fever with pains occurs in dengue, phlebotomus fever, trench fever, yellow fever, relapsing fever, small-pox, typhus, rat-bite fever and plague (hubo). (5) Fever with pink eyes occurs in measles, small-pox, plague, typhus, dengue, influenza, rheumatic fever, etc. (6) Fever with jaundice occurs in malaria (pernicious), relapsing fever, yellow fever, blackwater fever, infectious jaundice, infantile liver, pyæmic abscess, cholecystitis and pneumonia. (7) Fever with œdema occurs in hookworm infection, nephritis, oroya fever, etc. (8) Fever with relatively slow pulse occurs in enteric fever, undulant fever, dengue, phlebotomus fever, trench fever, cerebro-spinal fever, yellow fever (2nd day) and schistosomiasis. (9) Fever with rapid pulse occurs in tuberculosis, trypanosomiasis and many of the infectious diseases. In this connection other common causes of tachycardia should be borne in mind, *viz.*, exophthalmic goitre, nervousness, excitement, tobacco, myocarditis, pneumogastric irritation and administration of drugs like thyroid, belladonna, etc. (10) Fever with leucopenia occurs in enteric fever, kala-azar, undulant fever, tropical splenomegaly, splenic anaemia, acute miliary tuberculosis. (11) Fever with leucocytosis occurs in leukaemia, suppurative processes, pneumonia, meningitis, plague, relapsing fever, typhus, etc.

(C) *Laboratory investigations.* (1) First examine the blood films for malarial parasites, leishmania, the spironema of relapsing fever, micro-filariae, and trypanosomes. The smear also helps the diagnosis of leukaemia and anaemia. A differential count may show eosinophilia which occurs in asthma, skin diseases and helminthic infections. Increase of large mononuclear leucocytes occurs in malaria, dengue, yellow-fever and trypanosomiasis. Lymphocytes are increased in kala-azar and tuberculosis. A total blood count is also very helpful. (2) If the clinical examination suggests infection with organisms of the enteric group, septicæmia, plague, undulant fever, etc., early blood culture may settle the diagnosis. (3) If the smear examination and culture of blood fail to detect any organism, the blood is tested for specific agglutinins during the 2nd week as the case proceeds. It is well, however, that agglutination tests be performed as early as possible for, in persons protected by prophylactic inoculation, an increasing titre is the only evidence that these antibodies are the result of infection causing fever. For this, several estimations must be made. The test is of value in the diagnosis of enteric fever and undulant fever. Agglutinins for the various dysenteric bacilli appear too late to be of value in the early febrile stage. The Well-Felix reaction is

done in typhus, but it is not exactly an estimation of agglutinins. Complement deviation tests should be done in all prolonged cases even in absence of clinical evidence of syphilis. (4) Stool examination is of great value especially in dysentery, cholera, enteric, helminthic and other infections. (5) Urine is examined as a routine in every case. If necessary, it may be cultured. In blackwater fever it is tested for hæmoglobinuria. Hæmaturia may occur in severe infections like plague, yellow fever, small-pox, etc. (6) Sputum is examined in pneumonia, tuberculosis and other pulmonary affections. (7) Cerebro-spinal fluid is examined in meningitis and trypanosomiasis. (8) Gland puncture is made for diagnosis of bubonic plague, trypanosomiasis, filariasis or syphilis. (9) Spleen and liver punctures are made for the diagnosis of kala-azar. (10) Aldehyde and antimony tests are done for the diagnosis of kala-azar.

FUNCTIONAL TESTS. RENAL FUNCTION. The efficient working of the kidneys is known by the following tests: (1) Detection of abnormal constituents in urine such as protein, casts, etc. (2) Alteration of the physiological balance between the blood and urine and the demonstration of substances in altered proportions either in the blood or in the urine. (3) The eliminating power of the kidney as tested after administration of:—(a) Some natural substances such as water, urea, test meals; (b) some foreign substances such as dyes like phenolsulphone-phthalein or indigo-carmin.

I. DETECTION OF ABNORMAL CONSTITUENTS OF URINE BY CHEMICAL TEST.
Proteins: (a) *albumin*, (b) *globulin*. It has been found that the albumin-globulin ratio is usually found to be above 10 in cases of nephrosis and between 5 and 10 in acute nephritis. The ratio is low during the early stages of acute nephritis and it rises as recovery takes place. A ratio of below 5 indicates an advanced state of glomerulo-nephritis with urea retention and impaired renal function. Lawson found that a just perceptible trace by the boiling test corresponds to 0.1 gm. per litre, a distinct cloud corresponds to 0.5 gm. per litre and a heavy cloud indicates 2.0 gm. per litre or over. The presence of casts, blood, pus, etc., signifies a renal lesion.

II. ALTERATION OF PHYSIOLOGICAL BALANCE BETWEEN THE BLOOD AND URINE.

The blood urea clearance test. It is claimed to be the most sensitive test of renal efficiency at present available. When urine volume is large the rate of urea excretion is directly proportional to the blood urea content. Expressed in other words, the urea excretion per minute equals the urea contained in a constant volume of the blood; this volume in a normal individual is 75 c.cm. The direct ratio between the blood urea content and the urea excretion rate holds only when

the urine volume is about 2 c.cm. per minute in adults. When the urine volume falls below this limit, the urea excretion also falls and on the average in proportion to the square-root of the volume. These data led to the development of the urea clearance test. Two modes of clearance are recognised. The maximum clearance occurs when the flow of urine is above 2 c.cm. per minute and the standard clearance when the flow is below 2 c.cm. per minute. These two being calculated, the normal percentage is also determined.

No special precaution is necessary, the test being performed between breakfast and lunch. The patient is put to bed, a glass of water is given at the beginning of the test. (1) Blood for urea estimation is drawn a few minutes before the end of the first hour. (2) The total volume of urine secreted is accurately measured. The urine is collected at the end of one hour and again at the end of two hours and the concentration of urea is determined. The standard or the maximum clearance is then calculated in each hourly specimen. The normal clearance is next determined. The normal range is from about 70 per cent. upwards. In terminal stages of hæmorrhagic nephritis the urea clearance is below 20 per cent. of the normal. Uræmia is uniformly present if the urea clearance falls below 5 per cent. and is uniformly absent with figures above 10 per cent. In some cases of nephritis, values between 20 to 40 per cent. may be seen with a normal blood urea content, thus demonstrating the superiority of this test over the simple blood urea estimation.

Urea and non-protein nitrogen contents of the blood are held by most authorities to yield the most reliable information. In certain forms of nephritis as in the azotæmic type, in prolonged vomiting, intestinal obstruction and acute abdominal lesions, there is an increase in the non-protein nitrogen content of over 40 mgm. per 100 c.cm. of blood. A creatinin content constantly over 1.5 mgm. per 100 c.cm. of blood indicates permanent renal damage. With nitrogen retention, in cases of acute nephritis, the blood calcium falls as low as 6 mgm. per 100 c.cm. of blood or sometimes lower and the phosphorus content rises to 5 mgm. per 100 c.cm. of blood. Marked nitrogen retention occurs in chronic interstitial nephritis and little or no retention is found in chronic nephritis with œdema and lipoid nephrosis. Blood cholesterol is markedly increased (as much as 0.3 per cent. or over) in lipoid nephrosis and other conditions such as cholelithiasis.

In chronic nephritis with œdema and in lipoid nephrosis, the albumin falls to 2.5 per cent., globulin to 1.7 per cent. and the total protein to 4 per cent.

• *Volume and specific gravity.* The normal urine volume is 1,500 c.cm., Sp. Gr. 1,015 to 1,025. In acute nephritis the volume is 200 to 500 c.cm., Sp. Gr. 1,025 to 1,035. In chronic interstitial nephritis the volume is 2,000 c.cm. or over, Sp. Gr. 1,005 to 1,012. In lipoid nephrosis the volume is 800 to 900 c.cm., Sp. Gr. 1,020 to 1,025.

III. TESTS DEPENDING ON THE ELIMINATION OF SOME SUBSTANCE ADMINISTERED TO THE BODY.

1. *Water test* (Straus-Graunwald method) A pint of water is given to a starving patient and urine is collected at hourly intervals. Normally, the sum of the first three hours' specimen should be equal to the quantity of fluid administered, but if the quantity is less, it signifies a renal lesion.

2. *MacLean's urea concentration test.* Fifteen gm. of urea dissolved in about 5 oz. of water flavoured with tincture of orange are given to a patient who has had nothing to drink for some hours and after emptying the bladder The urine is passed in each of the subsequent three hours and urea concentration estimated. In the case of normal healthy kidneys the concentration in the second and third hours is usually over 2.5 per cent. and almost invariably over 2 per cent. With moderate damage of the organs, concentration from 1.5 to 2.5 per cent. may be met with and with severe lesion under 1.5 per cent.

Like all tests in which absorption of substances from the alimentary canal plays a part, it suffers from certain disadvantages. The urinary excretion of urea depends in this case not only upon the concentrating power of the kidney but also upon the rate of absorption which is controlled by the emptying time of the stomach since urea is absorbed from the intestines. The urea clearance test has largely replaced this urea concentration test.

3. *Renal test meal* Mosenthal employs a standard diet and collects two-hourly specimens of urine throughout the day. The specimens are examined for volume, specific gravity, urea and salt concentration. The following signs indicate renal lesion. (i) Fixed or low specific gravity. (2) Lowered output of salts and nitrogen. (3) Tendency to polyuria. (4) Loss of concentration in the night urine associated with low specific gravity and nitrogen content.

4. *Dye tests.* (a) *Indigo carmine test.* Ureteric catheters are introduced and 0.1 gm. of the dye is injected intramuscularly. The urine is tested in six to eight minutes. The intensity of the colour indicates roughly how much of the dye is excreted and any delay signifies renal inefficiency This test can detect a unilateral renal lesion and is useful in surgical cases. (b) *Phenolsulphone-phthalein test.* In order to secure a good flow of urine, the patient is given 300 c.cm. of water to drink and the bladder is emptied twenty minutes after and 6 mgm. of the dye in 1 c.cm. of sterile saline are injected intramuscularly. The dye generally appears in urine within ten minutes of the injection. The bladder is emptied after an hour exactly and again after two hours and the two specimens are preserved for the estimation of the dye colorimetrically in each. By the first hour 50 per cent and by the second hour 70 per cent. of the dye should be excreted. Anything below this points to renal inefficiency. By

ureteric catheterisation, the test can be applied to detect a lesion of each kidney separately.

5. *Pyclography*. See page 66.

HEPATIC FUNCTIONS. (A) *Investigation of the pigmentary functions*. A positive reaction of the blood to bile indicates a derangement of the hepatic function.

Van den Bergh reaction. McNee recommends the following classification of jaundice:—(1) Obstructive hepatic jaundice. Here bilirubin is reabsorbed into the blood and is subsequently excreted into the urine. (2) Haemolytic jaundice. Here more pigments are offered than the polygonal cells of the liver can actually dispose of resulting in their transference from the Kupffer cells to the blood stream again. (3) Toxic and infective hepatic jaundice. This is really a combination of these two conditions. Van den Bergh's reaction distinguishes between these varieties of bilirubin and indicates the type of jaundice. An immediate direct reaction indicates obstructive jaundice, a delayed direct reaction points to a haemolytic or non-obstructive type. The biphasic reaction is seen in cases of toxic and infective jaundice. The bilirubin content of normal serum is 0.2 to 0.5 units. Bile does not appear in urine until 4 units are present in the blood, but in haemolytic jaundice there is no bile in the urine though 5 to 18 units are present in the blood.

(B) *Investigation of the metabolic functions*. (a) *Nitrogen partition method*. Urinary nitrogen coefficient = $\frac{\text{Urea nitrogen}}{\text{Total nitrogen}}$. Normally the value of this coefficient is between 85 and 90, whilst in hepatic inefficiency it falls to 40 or 50, indicating a disease in the ureogenetic function. The values for amino-acids and the non-protein nitrogen in the blood increase in such cases.

(b) *Lævulose tolerance test*. By mouth 100 gm. of lævulose are given and during the following twenty-four hours specimens of urine are collected. If lævulose appears in urine about an hour after the administration of the sugar, there is hepatic inefficiency. Specimens of blood are also taken at half hour intervals and tested for sugar; a rise in sugar above 140 mgm. per 100 c.cm. of blood points to hepatic inefficiency. *Galactose tolerance test*. Normally the ingestion of 40 gm. of galactose causes no appreciable increase of blood sugar, but a hyperglycaemia is marked in cases of hepatic lesions as in catarrhal jaundice, cirrhosis, atrophy and neoplasms. *Sugar tolerance test*. This is useful in diabetic cases. The patient is not given an evening meal on the day preceding the test; 50 gm. of glucose (1.5 gm. of glucose per kilo. body weight) dissolved in about 400 c.cm. of water and flavoured with syrup of orange are given to the patient. Blood sugar per 100 c.cm. and urine sugar per cent. are determined at intervals $\frac{1}{2}$, 1, 2 and 3 hours. The normal blood sugar before the test is 80 to 120 mgm. per 100 c.cm. of blood. Within an hour after taking

glucose the blood sugar rises to 130 to 180 mgm. per 100 c.cm. representing the highest figure. Blood generally returns to normal within two to two and a half hours. Urine should not give any reaction for sugar.

In mild diabetic cases, the resting blood sugar is higher and after the administration of glucose, the content rises above the threshold value of the kidneys. In renal glycosuria the blood sugar content is always below the normal level.

(C) *Investigation of the hæmopoietic functions.* (a) The coagulation time of the blood is said to be increased in hepatic derangements. The fibrinogen content of the blood is decreased in hepatic inefficiency.

(b) *Widal's test.* Generally a meal is followed by leucocytosis and this reaction depends on the functional integrity of the liver. In deranged hepatic functions, the reaction is either a leucopænia or there is no rise in the content.

(D) *Investigation of the global capacity.*

Phenoltetrachlorphthalein test. The dye which is obtained in ampoules is injected intravenously, 5 mgm. per kilo., in about 250 to 300 c.cm. of normal saline. Exactly after a quarter of an hour, and again at the end of one hour, 5 c.cm. of blood is drawn out. The amount of dye present in each specimen of serum is determined colorimetrically. In normal persons from 2 to 6 per cent. of the dye remains in the circulation after 15 minutes and nothing remains at the end of one hour. In hepatic disorders there is an appreciable amount retained in the blood after one hour.

(E) *Investigation of the duodenal contents.* Lyon has devised a method by which the functional integrity of the biliary passages can be tested. A fasting patient is made to swallow a duodenal tube and bile is aspirated at intervals before and after injecting in the tube 50 to 100 c.cm. of 25 per cent. magnesium sulphate solution which causes the gall bladder to contract and empty itself. Bacteriological and cytological examinations of the samples of bile aspirated give reliable information as to the inflammatory and infective conditions of the various parts of the biliary tract.

(F) *Cholecystography.* See page 66.

PANCREATIC FUNCTIONS. Derangement of pancreatic function is accompanied by disturbances of carbohydrate metabolism and definite alterations in the digestive and absorptive processes of the body. Diminished or absent external secretion of the organ is marked by the presence of undigested protein, excessive quantities of fat and free starch in the fæces. Microscopical and chemical tests are resorted to to detect these substances in the fæces and to test the efficient working of the organ.

Loewi's test is a clinical test to detect a lesion of the pancreas. This is due to disturbance in the normal antagonism between the suprarenals and the pancreas. The disordered^{pan} pancreas excites the sympathetic and the dilatation of the pupil occurs in response to the

local action of adrenalin. Two drops of adrenalin chloride are instilled into the conjunctiva and dilatation of the pupil is noticed within a short time. This is characteristic of a pancreatic lesion and is not seen in normal subjects.

Diastase test. The normal diastatic index of urine is between 6.6 and 30. A fluctuation of the figure provides a very useful guide to diagnosis. Pancreatic lesions are always accompanied by an increased diastatic index of urine. Acute inflammatory conditions of the organ (acute hæmorrhagic pancreatitis) show a considerable increase of the figure to 100, 200 or sometimes even higher. The figure may or may not be affected in chronic pancreatitis, and varies between 10 to 50. In cases of neoplastic conditions of the pancreas, it is 30 to 100.

Besides the tests mentioned, certain clinical signs and symptoms are characteristics of pancreatic lesions depending on the involvement of the anatomical structures around the organ. A tumour in the head of the pancreas compresses the common bile duct and gives rise to obstructive jaundice. Irritation of the adjacent solar plexus in acute pancreatitis gives rise to pain in the epigastrium and back, vomiting and shock.

GASTRIC FUNCTION. TEST MEALS. One of the methods of investigating the gastric function is by studying the response of the stomach to test meals. The common ones are, one hour method (Ewald), and fractional method (Rehfuess).

Ewald's method. The examination is conducted in the morning, the patient having fasted from 9 p.m. the night before the examination. The test meal which consists of a pint of tea and a small piece of toast (about $\frac{1}{2}$ oz.) is given at 7 a.m.; at 10 a.m. a gastric tube is passed and as much fluid as possible is aspirated from the stomach. The total quantity of the aspirated fluid is measured, its general appearance is studied and noted and then the fluid is sent to the laboratory for qualitative and quantitative examination for the detection and estimation of the presence of (1) free HCl, (2) organic acids, e.g., lactic acid, acetic acid, butyric acid, (3) blood, and (4) total acidity.

The composition of the gastric content after a test meal depends upon the volume and nature of fluid in the stomach at the time of giving the meal, volume and nature of the meal, rate of gastric secretion and its amount and lastly the condition of the pylorus. All these factors vary and it is impossible to obtain anything like comparable results with this method at the end of one hour. Ewald's method, therefore, has now been replaced by the other method which aims at giving a true estimate of gastric function.

Rehfuess method. The patient is given a light supper (a glass of milk and a charcoal biscuit) the night before. The following morning before any food is taken, the patient is made to swallow a Ryle's tube. The tube is marked by one transverse line at 40 cm. to indicate the cardiac orifice and by three transverse lines at 57 cm. to indicate the

pylorus. The tube is swallowed till the pyloric mark almost touches the teeth, the fasting stomach contents are then aspirated through the tube with a 20 c. cm. record syringe till the stomach is completely emptied. The quantity of the resting juice is measured and noted. If the volume aspirated be less than 20 c. cm., it is likely that the total fluid has not been recovered. The injection of a syringe of air in many cases will lead to a more complete evacuation. The test meal is made by boiling one ounce of oatmeal in a quart of water until the bulk is reduced to one pint. The preparation is then strained and may be flavoured with little salt. Immediately after emptying the stomach, one pint of the test meal is given to the patient to drink; 15 c. cm. specimens are aspirated every 15 minutes for 2½ hours or until nothing further can be aspirated. The specimens are collected in separate clean test tubes which are duly labelled and serially numbered 1st, 2nd, 3rd, etc., and then all the tubes including that containing the fasting juice are sent for analysis. Each specimen is examined for the presence of blood, bile, mucus, starch, free HCl; and estimation of free HCl and total acidity is carried out. The emptying of the gruel meal is indicated by the absence of reaction for starch in the specimen.

Fractional test meal interpretation. Normal resting juice. No charcoal, free HCl is very low (from 0 to 20)—volume varies between 10 and 150 c. cm. with average of about 54 c. cm. *Later specimens.* *Acidity.* The first specimen after the test meal shows very low HCl (lower than that in resting juice), then there is a gradual increase in concentration up to the 5th or 6th specimen (1½ to 1¾ hour after meal) rarely going above 40. After this, there is a gradual diminution in the HCl content. This fall is frequently shown by the appearance of bile in the specimen. *Total acidity* is usually 10 to 25 c. cm. N/10 per cent. higher than the free HCl and consists mainly of organic acids such as lactic and butyric. *Blood and mucus*—nil. *Motility.* The usual emptying time of the gruel is from 1½ to 2½ hours.

In gastro-duodenal ulcer the typical climbing curve is seen. The fasting stomach may contain about 30 c. cm. of juice, may be slightly bilestained, with no food remnants or charcoal. Free HCl is in high concentration. Later specimens show diminution of free HCl and total acidity. Afterwards both increase steadily and go considerably above normal even up to 70 or 80 on an average. The bile is absent owing to absence of regurgitation; there is no blood nor mucus.

In chronic cicatrising gastric ulcer with pyloric obstruction, the fasting stomach may contain about 70 c. cm. of the fluid; traces of bile and charcoal are seen from the previous day; free HCl is moderate, but total acidity is rather high. *Later specimens.* *Acidity.* Free HCl climbs to a continued plateau of moderate concentration. Total acid is proportionately rather high; bile is present in traces or absent in later specimens; blood is absent; mucus is normal. *Motility.* As much as 170 c. cm. of fluid containing much gruel may be present even 3½ hours

after the meal showing obvious pyloric obstruction. Ulcers in other parts of the stomach do not give such typical pictures.

Duodenal ulcers may cause very little abnormality in the curve, frequently, however, there is a high concentration of HCl with a rapid emptying time of the stomach.

Carcinoma of the stomach. The fasting stomach contains about 40 c.cm. of fluid which is very foul smelling, dark coloured and contains altered blood; mucus and charcoal are present from the previous night. No free HCl. Total acid is relatively high. *Later specimens.* *Acidity.* Free HCl and total acid are rather above average concentration or kept at a uniform low level with free HCl absent throughout; bile is absent, mucus is normal, and blood is present. The meal leaves the stomach rather rapidly.

Achylia gastrica or achlorhydria. Fasting stomach contains only a few c.cm. of the juice, a trace of bile and no free HCl. The total acid is very low. Later specimens show complete absence of HCl; total acidity is also very low. Bile is present in later specimens, mucus is absent and blood is absent. The whole meal leaves the stomach very quickly, i.e., in about an hour. The graph is represented by a straight line.

FURUNCULOSIS. Boils or furuncles are acute circumscribed staphylococcal infections about one or more hair follicles. The infecting organisms are generally *staphylococcus pyogenes aureus* but in some cases these are *staphylococcus pyogenes albus*. The condition may start as impetigo and infection subsequently takes place along the hair follicles. Crops of boils appear when the body resistance is considerably lowered to staphylococcal infections. The glycosuric soil affords a suitable medium for staphylococci and a gouty seborrhœic acid soil or a diathesis of a sluggish metabolism is also a very fertile one for boils to grow. Of the predisposing factors, faulty dietetics with an avitaminous regime and intake of excess of carbohydrates, excessive tobacco smoking and a mode of life with insufficient muscular exercise, deserve mention. Alcoholic drinks especially champagne, due to some deleterious by-products of partial fermentation, often favour the infection. Besides, anæmia, renal disease, debility and chronic constipation predispose to furunculosis. General debility may be theoretically regarded as an invitation to staphylococci though boils are generally met with in over-fed bulky persons. Psychic states such as anger, emotion, irritation, etc., play an important ætiological role. In these states, both adrenalin and sugar are poured into the blood stream and as these are not utilized, they favour the growth of the bacteria. Chronic intestinal toxæmia and hidden septic foci in the body also favour infection. Endocrine dysfunctions and calcium deficiency are also potent ætiological factors. A boil appears as a hard, tender, circumscribed mass which later suppurates and discharges pus

leaving a central necrotic core. The axillæ, forearms, glutei and face are the sites of selection. Boils on the face and particularly over the upper lip might sometimes precipitate a secondary cerebral infection which generally proves fatal.

TREATMENT. A thorough search should be made for septic foci which when found should be eradicated. Diabetes, albuminuria and chronic constipation should be treated on the usual lines. Flushing of the intestinal canal and subsequent starvation lessens toxæmia and is often successful in aborting an attack. A cautious dietary with abundance of vitamins and restricted intake of meat and sugar, considerably helps the treatment. Fresh yeast, a tea-spoonful, thrice daily, often acts well in furunculosis but this should not be given during vaccine therapy. A mixture of dilute sulphuric acid 5 min., with sulphate of magnesia 1 dr. is often efficacious. Sublimed sulphur in $\frac{1}{2}$ to 1 dr. doses or fresh calcium sulphide in $\frac{1}{2}$ gr. doses, may also be prescribed. The affected region should be frequently washed with weak solution of perchloride of mercury 1 in 2000, or 2 per cent boric lotion to prevent an auto-inoculation. During the early stages before suppuration takes place boric fomentations, compresses of glycerine and ichthyol or glycerine of carbolic are very effective in alleviating the acute throbbing pain. A boil may often be aborted by the application of a mercury and carbolic plaster with a small hole in the centre. In all cases, squeezing is not only a bad but a dangerous practice, as this often helps the dissemination of the organisms into the blood by breaking the protective loculi in the region where the cocci are lodged. This also adds to the inflammatory mischief in the tissues. When the boil is mature and the pus is ready to escape, under proper aseptic precautions, evacuation of the septic materials may be effected with a knife. Correction of faulty metabolism and calcium and endocrine therapy is also useful in the treatment. Intramuscular injections of collosof manganese $\frac{1}{2}$ to 1 c.cm., twice a week, help the retrogression of furuncles. Stannoxyd tablets, one tablet thrice daily, are also prescribed in some cases. Ultra-violet therapy, baths, etc., are also of proved value in the treatment of furunculosis.

Vaccine therapy (see page 773) has given encouraging results in the treatment of furunculosis, the autogenous type being generally better than stock vaccine. A single dose of vaccine if administered early, tends to abort an acute boil. The dose should be 1000 million of mixed staphylococci. An average initial dose, in ordinary cases should be 100 millions of *Staphylococcus aureus*, gradually increased to 250 millions at intervals of a week. To prevent a relapse, it is advisable to prolong the vaccine therapy for some time after apparent cure.

It is suggested that there is some connection between the oxidising action of potassium permanganate and the thyroid in that they act by tending to sway the pH of the blood. It appears that boils occur in those parts of the body where there is likelihood of local

acidosis. Ball, with his favourite prescription for boils containing sulphate of iron 3 gr., sulphate of magnesium $\frac{1}{2}$ dr., dilute sulphuric acid 10 min., solution of hydrochloride of arsenic 2 min., chloroform water to $\frac{1}{2}$ oz., advocates a tabloid containing thyroid $\frac{1}{2}$ gr. and potassium permanganate $\frac{1}{8}$ gr., in cases of intractable boils. The mixture and the tablets are given three times a day. He reports considerable success with these drugs.

Oxygen injections (Salzmann) have given very gratifying results in cases of furuncles and paronychia. The oxygen, under high pressure $\frac{1}{2}$ to 1 atmosphere, is introduced into the centre of the furuncle through a sterile glass cannula or a fine injection needle. In the course of a day, 5 to 10 such injections may be given, as needed. The tissue of the furuncle softens with astonishing rapidity, so that the furuncle is emptied spontaneously within 24 to 48 hours. Furuncles of the nose and upper lip especially may be similarly treated and leave no disagreeable complications.

GASTRIC AND DUODENAL ULCERS. During the last twenty-five years ideas on the subject of gastric and duodenal ulcerations have been radically revised mainly as a result of the progress of abdominal surgery and modern X-ray methods of diagnosis. Clinicians now realise how unreliable were the signs and symptoms on which they had to base their opinions. Radiology has enabled a diagnosis of ulcer to be made in many cases which previously might have been termed gastritis. Ulceration is sometimes seen not only without pain but actually without any sign of indigestion.

The incidence of peptic ulcer, under which term are included both the gastric and the duodenal forms, has been recently studied in many series of cases. Duodenal ulcer is very much more common than gastric ulcer and occurs more frequently in males than in females. The disease may occur at any age, though cases under twenty years of age are very uncommon. Patients have often suffered from abdominal symptoms for many years before coming under treatment, and it is therefore difficult to be certain when the disease really started.

In spite of the large amount of experimental work that has been carried out in recent years on the pathology of peptic ulcer, it must be admitted that the cause of the condition is still undecided.

Various factors have been thought to be responsible for the causation of the ulcer. The gastric juice or perhaps its hydrochloric acid content may in some way be responsible as ulcers occur in such situations as are exposed to its action, e.g., the stomach, the first part of the duodenum, and last part of the oesophagus and in the jejunum of cases where gastro-jejunostomy has been performed. Interesting experimental work by Bolton confirms the fact that the acidity of gastric juice and pyloric obstruction are factors in the production of peptic ulcers.

Of recent years great stress has been laid on the importance of focal infection as a cause of peptic ulcer. The experimental work of Rosenow in America lends support to this. By inoculation of streptococci obtained from infected teeth of ulcer patients, he claims to have produced gastric ulceration in animals. Although this is not absolutely convincing it is reasonable to suppose that chronic sepsis such as may occur around the apex of a tooth or in a chronically inflamed appendix or gall bladder may play a part in the establishment of gastric or duodenal ulcer. The work of Bolton has demonstrated in animals that the introduction of septic materials into the stomach is followed by the formation of ulcer. Alvarez (1932) is not satisfied with any of the theories of causation of ulcer and particularly with the infection theory. He suggests that the importance of psychical factors has been overlooked and that ulcer commonly appears in persons who live under nervous tension.

Sometimes the ulcer results from auto-digestion of a portion of the stomach wall from which the blood supply has been cut off by a minute embolus lodging in an artery. The presence of a foreign body in the stomach, erosion of the gastric mucosa by strong acids and alkalies are also important ætiological factors. Anæmia, chlorosis, chronic colitis and gastritis associated with hyperchlorhydria are important predisposing factors. Besides there may be gastric ulcer diathesis, as gastric ulcers tend to run in some families and duodenal ulcers in others.

Ulcers may be acute or chronic and the symptoms of the two conditions are different. Acute ulcers are generally multiple, small and superficial. Hæmorrhage is common but rarely fatal. A chronic ulcer is usually single and irregular in shape with an indurated edge. It is usually found near the pylorus on the lesser curvature towards the posterior surface of the stomach and the symptoms are periodic and intermittent, the chief being pain, vomiting, and hæmatemesis. The pain is characteristic, its onset is most punctual in the same patient after the same meals and it appears with the most exact regularity after the same interval of comfort. The periodicity of pain is altered by variation in the quantity and quality of the food and by irregularity of meals. It is complained of in the epigastrium coming on within half an hour to an hour after food and relieved by vomiting. The nearer the ulcer is to the pylorus the lower down is the pain and longer its interval after a meal. In cases of duodenal ulcer, the pain continues until food is taken to relieve the pain. The definite relationship of pain to food intake has been described by Moynihan as follows: "In case of gastric ulcer, the pain which, after an interval, follows the taking of a meal, gradually disappears before the next meal. In cases of duodenal ulcer, the pain continues until the next meal, or until food is taken to give ease to a wearisome pain. The rhythm of gastric ulcer is 'food, comfort, pain, comfort,' and then again 'food,

comfort, pain, comfort'; of duodenal ulcer it is 'food, comfort, pain' and then again 'food, comfort, pain'; a quadruple rhythm in the former disease, a triple rhythm in the latter. The pain may be slight or intense and may radiate to other regions of the body. The actual cause of pain is uncertain. Some believe it to be due to the spasm of the muscles of the stomach. According to Hurst, tension is the cause of pain. Diffuse tenderness over the abdomen is present with a little rigidity of both the upper recti muscles. An area of cutaneous hyperæsthesia can be demonstrated in many cases. When the pain is delayed from one to two hours after food, the ulcer is probably a prepyloric one. If the delay is more than two hours, the ulcer is likely to be duodenal; it lasts till the next meal which usually gives relief for a definite period. When complications such as pyloric stenosis or perigastric inflammation, etc., set in, the pain becomes more continuous and the regularity of its onset in relation to food becomes lost. Vomiting directly after food is unusual in gastric ulcer. It sometimes comes on shortly after taking food and a definite interval elapses which may be longer or shorter according to the position of the ulcer. Hæmatemesis and tarry stools (melæna) may supervene as complications. Hæmatemesis may be absent in duodenal ulcer and altered blood may be passed as tarry stools (melæna). Of the other less important symptoms, secondary anæmia, the feeling of a definite tumour or thickening in the epigastrium, constipation, etc., deserve mention.

Apart from clinical study, the following methods are available for the investigation and diagnosis of gastro-duodenal ulcers:—(1) Ewald's test meal (see page 1357). (2) Fractional test meal (see page 1358). (3) Occult blood in fæces (see page 1477). (4) Radiography Examination of the stomach and duodenum by means of the X-rays after the ingestion of an opaque meal is very useful in the diagnosis of ulcers of these organs. Investigations should be made both under the screen and with photographs. The opaque meal used in the screen examination usually consists of 3 oz. of barium sulphate in half to one pint of milk. By this means the shape of the stomach and its filling properties can be investigated. The motor activity however and rate of stomach emptying are better studied with a more solid meal, such as porridge, or bread and milk containing barium sulphate. There should be no residue of such a meal in the stomach after six hours. Persistent deformity in the outline of the stomach or duodenum is the most reliable evidence in the X-ray diagnosis of ulcer. Thus in gastric ulcer the barium may be seen filling a niche in the wall of the stomach or there may be definite organic hour-glass appearance. In the duodenum a persistent alteration in the shape of the duodenal cap may be seen; X-ray examination will also reveal pyloric obstruction.

Variations in tone or in position of the stomach are not diagnostic of ulceration. Subsequent examination after administration of belladonna

is of value in distinguishing between constriction of the stomach due to spasm and that due to cicatrisation.

TREATMENT. The treatment of uncomplicated gastric ulcers should always be medical. Before medical treatment is started, all sources of infection in the body so far as practicable should be eradicated. The teeth, throat and naso-pharyngeal regions should be thoroughly examined and proper treatment instituted. The difficulty lies with the intra-abdominal sources of infection which are not commonly discovered and the treatment is therefore greatly handicapped. The general principle of treatment of all ulcer cases includes complete rest in bed, careful dieting and the use of suitable antacids. In all cases the treatment is a prolonged one and requires the patient to be in bed from four to six weeks. A modified Sippy diet (see page 1340) is advisable with an alkaline powder after feeds, and olive oil, belladonna or atropin before the feeds. During the first two weeks feeds are given every two hours and consist of citrated milk (3 gr. of sodium citrate to an ounce of milk) or peptonised milk, Horlick's milk or Benger's food. The quantity should be small and should not exceed five ounces. The quantity and quality of the feeds are altered and improved during the subsequent weeks and are as follows. During the third week raw eggs, thin bread, butter and cream may be added to the previous diet and are given every two hours as before. During the fourth week the feeds are given every two and half hours and consist of five ounces of citrated milk alternated with feeds composed of potato soup, arrow-root or milk pudding. During the fifth week the milk feeds are reduced and additions are made to the dietary in the form of pounded fish 2 oz., lightly boiled egg and crisp toast with butter. The feeds are allowed every 2½ hours. The same regime is carried on up to the 8th week. With these feeds measures are adopted to diminish the secretion and the strength of the resting gastric juice. Immediately before the three feeds ½ an oz. of olive oil is given and directly before three other feeds, tincture of belladonna 5 to 10 min. with chloroform water ½ oz. or sulphate of atropine 1/200 gr. in 1 dr of water is given to the patient.

In cases of acute ulceration associated with hyperchlorhydria, attempts should be made to neutralise as far as possible this acidity. Alkalies should be chosen which will do this without causing a secondary secretion. It has been found that sodium bicarbonate is a strong agent in producing a secondary flow of hydrochloric acid. It is therefore physiologically wrong and even harmful to employ this drug in attempting to give rest to the ulcer from the effects of the acid. A good combination consists of carbonates of calcium, magnesium and bismuth each 20 gr.; 1 dr. of this powder in a little water is taken by the patient 1 hour after each feed during the day and two teaspoonfuls, the last thing at night. During the third and fourth weeks a teaspoonful of this powder is taken three times a day after

feeds, and two teaspoonfuls at night. During the 5th to 8th weeks a teaspoonful of powder is taken twice a day after feeds and 2 teaspoonfuls at night. The mouth should be well cleansed with some alkaline water after each feed. During such treatment tobacco, alcohol, tea and coffee should never be indulged in. When the radiogram indicates that the ulcer has healed after the treatment, the pain and other clinical symptoms have subsided and the occult blood test (stool) is negative, the patient is allowed up for gradually increasing periods and more additions are made to the dietary. Besides those contained in the previous diets, eggs, honey, apple-jelly, fresh fish (boiled or steamed), chicken or mutton, custard pudding, are added. The feeds are given every 2½ hours and one teaspoonful of the alkaline powder is taken after breakfast and 2 teaspoonfuls last thing at night and the olive oil or belladonna before breakfast, lunch and dinner. In the tropics the main ulcer diet should consist of soft rice and milk. After this the diet should be liberal and vegetables, fish, minced mutton, boiled or roast chicken and sweets may be added to the dietary. The breakfast, lunch and dinner should be small meals, well chewed and eaten slowly. The patient should always rest for some time after meals.

Rich condiments should never be added to the dietaries, which should always be unstimulating so as not to invoke gastric secretion. The food should be poor in protein and rich in carbohydrates and fats, of sufficient caloric value and served as small feeds so as not to over-distend the stomach.

Lenhartz diet. Lenhartz advocates 8 oz. of milk mixed with one egg for the first 24 hours after which the quantity is increased daily by 3½ oz. of milk and 1 egg until 2 pints of milk and about 8 eggs are reached. From about the third to the eighth day, raw minced meat starting with 1 oz. in divided doses is given. If well borne, boiled rice, pounded fish or chicken are later allowed and the number of eggs are reduced. At first feeds are given at hourly intervals and complete rest is allowed at night. Both the eggs and milk are iced and the eggs beaten up whole. By the end of the fourth week the patient is put on a mixed diet containing the common foodstuffs avoiding indigestible ones. While carrying out the Sippy treatment, the precipitation of alkalosis should always be borne in mind. The common symptoms are headache, giddiness, nausea, vomiting, drowsiness, tetany or coma; the pulse is rapid and respirations are slow. Alkalies should be stopped, sufficient glucose should be taken by mouth or 1 oz. of glucose in 8 oz. of normal saline should be administered per rectum six hourly. Intravenous injections of calcium are also advocated in these cases.

Protein therapy. The injections of protein preparations were begun after dietetic treatment had failed. The injections were made intravenously, beginning with doses of from 0.2 to 0.4 c.cm. and gradually increasing to 1 or 2 c.cm. The injections are given at intervals of

3 to 4 days. A series consisted of from 4 to 8 and rarely 12 injections. A slight increase in temperature resulted in some cases, but no local reactions such as gastric pains and hæmorrhage were observed. The results obtained with this form of treatment are very favourable.

Indications for surgical treatment. (1) If symptoms persist after prolonged medical treatment and frequent relapses occur after apparent cure as in chronic ulcers. It is stated by Leube that if there be no relief of symptoms four to five weeks after medical treatment, surgical aid should be sought. (2) If profuse hæmatemesis sets in. (3) If acute perforation with general peritonitis supervenes and the pain is persistent due to perigastric adhesions, hour-glass stomach, stenosis of the cardiac or pyloric orifice and gastric dilatation.

After treatment. The patients with gastroduodenal ulcers must observe certain dietetic rules for at least six months, preferably one year and some care in diet is to be taken for the rest of his life.

The following rules are to be observed:—

1. Avoid longer intervals than two to two and a half hours without some form of food, *e.g.*, milk, eat slowly, bite and chew all the food thoroughly. Try to be free from anxiety during the meals.

2. Avoid highly seasoned food, cooked cheese, lemon juice, lemon peel (marmalade), pickles, spices, vinegar, acid fruits, strong tea, coffee or cocoa, rough foods specially celery, raisins and coarse vegetables, very hot food, specially meat soups, fruit with pips, *e.g.*, currants, figs, raisins, lettuce, raw apples, and any alcohol on an empty stomach.

3. Take specially raw or very lightly boiled eggs, milk, custards, jellies, sieved vegetables, bread, butter, cream, soft puddings, fish (not very salted), plain biscuits, cake, toast, rusks (not new or wholemeal bread).

4. Take fish or meat only once a day, in small amounts, and preferably veal, lamb, rabbit or chicken, but avoid tough meat, 'high' game, bacon and pork. Light wine with food is allowable. Salt should not be taken in excess but is allowable in moderation. Smoke only in moderation and not before meals. Take pulv. triple carb. (Maclean) one teaspoonful three times a day twenty minutes after meals and once in the night if awake.

5. Avoid constipation and indiscretions in diet.

GLUCOSE THERAPY. (See page 46). Glucose is extensively used nowadays in therapy for its beneficial effects in many diseases. It is the best nutrition for the tissues and is a food for the vital organs of the body especially the liver and cardiac muscle and its administration adds to the daily caloric intake in the body. It improves the quality of the pulse by improving the ventricular filling of the heart, also raises the systolic blood pressure and thus enhances the peripheral circulation, promotes diuresis and combats acidosis and lastly it is said to increase the protective powers of the blood. The various routes resorted to for

the administration of glucose are oral, rectal, subcutaneous, intramuscular, intravenous and pediatric practice even advocates a peritoneal usage. Regardless of the method of administration, glucose undergoes identical metabolic processes in the body and entails very little work on the digestive apparatus. Althausen asserts that the human body usually requires 8 gm. of glucose per kilo. body weight to meet the carbohydrate demand of the body. It is suggested that hypoglycæmia below 30 mgm. per cent. is generally incompatible with life. Besides its storage in the liver and muscles, glucose is also said to be stored in the skin. During prolonged strain and starvation the glycogen reserve of the liver may be completely exhausted though blood sugar and muscle glycogen remain practically constant. Lesions causing starvation states tend to depress the power of the body to utilise glucose. Regarding the strength of the solution to be used intravenously it has been suggested that a 4.9 per cent. solution in water has the same osmotic pressure as 0.85 per cent. sodium chloride solution and is therefore isotonic with the blood and tissue fluids. Hæmolysis of red blood cells was marked when a concentration below 3½ per cent. was used. A 25 per cent. solution is used for intravenous administration, a 10 to 15 per cent. solution is advocated for intramuscular use and a 5 per cent. solution has been injected intraperitoneally. A 20 per cent. solution when injected intramuscularly causes a local reaction. When glucose is injected into the tissues, absorption is marked in an hour's time. Authorities differ on the absorption of glucose from the rectum though it is often administered as such. A 10 per cent. solution has been found to be absorbed from the colon a little faster than an isotonic 5 per cent. solution.

Though deaths are rare, severe reactions are sometimes seen to follow the intravenous administration of glucose. The syndrome of nausea, restlessness, muscle tremors, rigors, convulsions, collapse, stupor and coma, described by Rowntree, is supposed to follow the administration of large quantities of the solution. The rate of intravenous injection should not exceed 4 c.cm. per minute of a 25 per cent. solution lest it produces an overstimulation of the endogenous insulin causing a hypoglycæmia. Reactions are seen to occur after the lapse of variable periods regardless of the dosage or the percentage of the solution used. Other untoward symptoms met with are acute cardiac dilatation from injecting a considerable amount of fluid at a time, apnoea, vomiting and diarrhoea and a few deaths have been recorded from pulmonary emboli. Technical errors and chemical impurities taken up by the solution from the rubber tubing during administration are claimed to be potent causes resulting in such reactions. Nitrogenous bacterial toxins called 'pyrogen' generated by bacteria present in insufficiently distilled water are held to be another cause. The water used for dilution of glucose solution should always be sterile and double-distilled. The reaction due to the rubber tubing can be overcome by soaking it in

soap and water for an hour, washing well with water and lastly soaking it again for four hours in 4 per cent. solution of sodium hydroxide and again washing the whole in distilled water.

THERAPEUTIC USES. Glucose is always indicated and extensively used before all operations particularly where the hepatic functions are deranged, the metabolic rate is high and the patient is undernourished. Glucose is of particular value where a blood transfusion is impossible. It has marked beneficial effects in cases of shock. Glucose should not be given in the early hours of the morning when the liver activity regarding the metabolism of glycogen is at its height. The best time for the administration of glucose is in the afternoon when the blood sugar level is at its lowest. During the rigid dieting regime in *obesity*, glucose should be freely given by mouth, to supply the necessary energy to the body. It is strongly indicated in cases of *ketosis* or *acidosis* and *hypoglycæmia* especially after overdosage with insulin. During prolonged *high febrile states* accompanied with tissue destruction a free intake of glucose with a sparing one of protein is advisable. In *toxæmias of pregnancy* such as *hyperemesis gravidarum* and *eclampsia* glucose therapy is most useful. In *cyclic vomiting* in children glucose with insulin overcomes the accompanying acidosis. The distressing symptoms of *sea-sickness* are very often relieved by glucose. It serves as an emergent food in *physical exhaustion*. Glucose combined with insulin is invaluable in *diabetic coma* where ketone bodies are excessively formed due to defective fat metabolism. In *toxæmias of acute infective fevers* such as *pneumonia*, *diphtheria*, etc *sepsis* and *severe burns*, glucose is said to dilute and neutralise the toxins. Glucose should always be administered in cases where the liver is liable to be damaged by toxins and after prolonged *anæsthesia*.

HÆMORRHAGE. Hæmorrhage denotes an escape of blood from the blood vessels of the body. It may be arterial, venous or capillary. When the blood is escaping from an artery, it is bright red in colour and escapes from the wounded artery in a series of jerks, synchronous with the heart beats. The loss of blood is considerable and rapid and the force and character of the hæmorrhage change with the fall of blood pressure. In hæmorrhage from veins, the blood is dark red or purple in colour and generally escapes in a smooth even stream, uninfluenced by the heart beats. In capillary hæmorrhage, there is a continuous oozing of dark blood from a cut raw surface which coming in contact with the oxygen of the air becomes bright red. Hæmorrhage may be external, when blood escapes from the body and internal or concealed, when the bleeding is proceeding from some region of the body in which it is not often easily detected. The bleeding in primary hæmorrhage occurs immediately after the division of a blood vessel, in the reactionary type, the hæmorrhage recurs within 24 hours of hæmostasis while in secondary hæmorrhage, generally caused by

infective processes in a wound, the bleeding starts after the first 24 hours, usually 8 to 10 days after the infliction of the wound. General constitutional symptoms after hæmorrhage are due to loss of a large amount of blood from the body. Signs such as pallor, loss of consciousness, subnormal temperature with blanched skin, shallow rapid respirations, restlessness, etc. supervene as a result of cerebral anæmia with subsequent failure of function of the vital centres of the brain. Intense thirst is complained of due to dehydration of the tissues of the body. Children and old people stand loss of blood badly and regeneration is much more prolonged than that in young adults. As an immediate after-effect of hæmorrhage, the following changes take place. There is generally no change in cell counts or the percentage of hæmoglobin within two hours after hæmorrhage. The vascular system adapts itself to the loss of blood by contracting, thus a diminution of the vascular area occurs. The diminution of hæmoglobin, red cells and blood protein does not reach its maximum for two weeks. The prognosis is grave if the percentage of hæmoglobin is below 25 per cent. Four hours after a hæmorrhage, there is an increase in the leucocytes of the blood and this may persist for a week. Within 48 hours the platelet count reaches the maximum. The cell increase is more rapid than the hæmoglobin increase which accounts for the colour index being below 1 in hæmorrhagic anæmia. The blood volume usually comes back to normal in six weeks, but in severe hæmorrhages the recovery time is much more prolonged. The specific gravity of the blood is lowered in all hæmorrhages.

CLASSIFICATION OF HÆMORRHAGES. *Group I.* Hæmorrhages due to injuries or localised diseases such as epistaxis, apoplexy, œsophageal varix, peptic ulcer, gynæcological conditions (placenta previa, postpartum hæmorrhage, ectopic pregnancy, etc.), hæmorrhoids and bleeding ulcerating tumours. *Group II.* Spontaneous hæmorrhage as a complication of a general disease. This includes acute infectious diseases such as septicæmia, measles, small pox, etc., jaundice, various forms of anæmia. *Group III.* The true hæmorrhagic diseases of the new born, purpura hæmorrhagica of Werlhof or thrombocytopenic purpura, hæmophilia, pseudohæmophilia.

GENERAL LINE OF TREATMENT. *Natural arrest of hæmorrhage.* In hæmorrhage from the medium-sized arteries, the contraction and retraction of the middle and inner coats may be sufficient to stop the bleeding. Sometimes a temporary arrest of hæmorrhage is brought about by the formation of clots at the mouth of the bleeding vessel. Changes in the blood such as an alteration of the specific gravity, an increase in the number of white cells and a fall in blood pressure associated with the shock of the injury, all help in the formation of clots. Ultimately a natural permanent arrest of hæmorrhage takes place by the formation of granulation tissue at the cut ends of the vessel.

In all emergency cases of accessible surgical hæmorrhage a temporary arrest of bleeding may be secured by the application of a tourniquet sufficiently tight to block the main artery supplying the part. Certain positions are advantageous in the procedure as in cases of bleeding from a limb, the latter should be elevated to empty it partially of blood and then bandaged with an elastic bandage. Other temporary measures include digital compression, ligature of the vessel, where convenient, compression with forceps, etc. The general treatment aims at promoting the rapid formation of internal clot in the bleeding vessel, procuring for the brain a sufficient amount of blood during the period of shock and supplying the necessary amount of fluid to the vascular system to maintain the blood pressure and lastly stimulating the hæmopoietic organs to replace the blood lost during hæmorrhage. The patient should be at complete rest with the foot end of the bed raised, directing the blood of the body towards the brain and if the hæmorrhage is severe the limbs should be bandaged to prevent stasis of blood in the dependent parts of the body. Restlessness should be controlled with an injection of morphia $\frac{1}{2}$ gr. In most cases the cause of death is the profound fall of blood pressure due to the loss of an excessive amount of blood from the body. As soon as the bleeding vessel is controlled, or sometimes even while doing this, intravenous administration of normal saline with glucose or a transfusion of blood becomes a necessity. Fluids may also be given by the oral, rectal and subcutaneous routes. Several pints of normal saline (1 dr. NaCl to a pint) at a temperature of about 100°F. must be administered per rectum till the blood pressure rises or about a pint or a half at a time may be injected subcutaneously into the loose, cellular tissues under the breasts or in the flanks. In the intravenous method of administration of fluids, the vein usually selected for operation is the median basilic vein of the arm. The fluid used is normal saline at the body temperature, the quantity being 2 to 3 pints at a time for an adult patient. The administration should be undertaken under strict aseptic measures. For detailed technique and precautions of blood transfusion see page 49. Drugs are of little use in the general treatment of hæmorrhage. Various preparations of ergot, given by mouth or injected hypodermically, have given good results especially in obstetrical and gynæcological cases. Intravenous injection of calcium chloride, 2 to 5 c.cm. of a 10 per cent. solution, is helpful in increasing the coagulability of the blood. Injection of whole blood 10 to 20 c.cm., hæmostatic serum 2 c.cm. or normal horse serum 20 c.cm. are also effective measures.

Diet has an effect on bleeding tendencies. Lipins and globulins which are contained in the liver, kidney, brain, egg yolk, bacon, nuts, beans and peas produce a definite increase of blood-clotting powers within twenty-four hours. A diet consisting of vegetables and low in food value such as cabbage, tomatoes, cauliflower and stewed fruit

will decrease the clotting power of the blood. Articles rich in iron are suitable for cases of secondary anæmia after hæmorrhage.

CAPILLARY HÆMORRHAGE. Considerable blood is sometimes lost by capillary oozing. *Treatment.* *Heat.* This may be applied in the form of hot water (115°F), cauterity at a dull red heat, etc. The drawback in case of a cauterity is that there is a chance of recurrence of hæmorrhage when the slough separates.

Cold. This is applied in the form of cold water or ice and is very effective in the treatment of hæmorrhage from the nose, mouth and throat. *Pressure.* Well graduated pressure as by plugging a wound from the bottom is very often effective in arresting a capillary oozing. Care should be taken not to devitalise a part during such a procedure. *Hæmostatics.* Local application of hæmostatics such as adrenalin, turpentine, compound tincture of benzoin, perchloride of iron, horse serum, coagulin, etc., are very often effective in checking local oozing from many parts of the body. Wright's styptic is an extract of the thymus or testis made with saline to which 5 per cent. of calcium chloride and a trace of sodium carbonate are added with 1 per cent. phenol as a preservative. The styptic is applied locally. The wounds should be well dried before the application of hæmostatics.

HÆMATEMESIS. Vomiting of blood may be due to various causes. The common sources include gastro-duodenal ulcer and œsophageal varices resulting from the chronic passive congestion of the portal circulation and cirrhosis of the liver. Gastrostaxis or gastric oozing from a local lesion in the stomach is also an occasional cause of profuse hæmorrhage. Coffee-ground vomiting is characteristic of gastric carcinoma. Aneurysm of the aorta by leaking into the œsophagus may cause hæmatemesis. Serious hæmatemesis may also occur in enlargement of the spleen especially in Banti's disease and thrombosis of the splenic vein. Mechanical injury and corrosion of the gastric mucosa by corrosive poisons are also important causes. The general toxic causes include poisons such as arsenic and phosphorus and toxins of various diseases such as acute yellow atrophy, infective and toxæmic jaundice, small-pox, malaria, yellow fever, hæmorrhagic disease, etc. A slight degree of hæmatemesis is not infrequently associated with vomiting of sea sickness, cyclical vomiting, post-anæsthetic vomiting, pernicious vomiting of pregnancy and acute intestinal obstruction. The vomited blood in hæmatemesis might not originate in the stomach itself but may have been swallowed as in cases of epistaxis, a bitten tongue in epilepsy or from bleeding gums.

In hæmatemesis, giddiness and faintness precede the actual bringing up of blood, the blood is dark in colour, clotted and often mixed with food materials. It is usually acid in reaction.

Treatment. The treatment of hæmatemesis is essentially that of its primary cause. If the source of bleeding is easily detected, it may be controlled under aseptic surgical measures. Usually a gastro-duodenal

ulcer is a common cause of hæmatemesis. The bleeding may be profuse and prove rapidly fatal. Such a hæmorrhage may be capillary, venous, or arterial. Medical treatment should always be tried first in case of hæmatemesis from acute gastric ulcer. Absolute rest should be imperative. The patient should be laid horizontally and an ice bag may be applied to the epigastrium. No food or stimulant should be given by the mouth but small fragments of ice or sips of iced water may be allowed at times. Morphia $\frac{1}{4}$ gr. may be administered hypodermically to calm the patient and as much as 1 gr. of the drug may be administered in 24 hours. A rectal injection of normal saline (about 4 to 6 oz.) containing 4 dr of glucose may serve as nutrition to the patient and may be repeated every 6 hours. Hæmostatics like horse serum 10 c.cm., coagulin 5 c.cm., etc., may be injected intramuscularly. Intravenous injection of a 10 per cent. solution of calcium chloride in 5 c.cm. doses is very often effective. Styptics such as adrenalin chloride (1 in 1000) 10 to 15 min., or turpentine oil 5 to 10 min. by mouth, are also advocated in these cases. When there is considerable loss of blood, transfusion is of particular value.

HÆMOPTYSIS. The term hæmoptysis or the spitting of blood is employed to indicate bleeding from the lungs or the respiratory passages. It may be true or spurious. When true, the blood is derived from the larynx, trachea, bronchi or lungs whereas in spurious hæmoptysis, the source of bleeding is above the larynx. The commonest cause of hæmoptysis is pulmonary tuberculosis. It may also occur in pneumonia but the sputum is usually rusty in colour. Pulmonary infarction is another cause of hæmoptysis. Passive congestion from heart disease, especially mitral valvular disease, is a cause of repeated bleeding from the lungs. Rarer causes of pulmonary hæmorrhage are abscess, gangrene, hydatid disease and neoplasm. Ulcerations of the larynx trachea, or bronchi also cause hæmoptysis. An aneurysm may leak into the trachea or a bronchus and the blood may be spat out. In bronchiectasis, a brisk hæmorrhage may occur. Among the rarer general causes of hæmoptysis are hæmorrhagic fevers, scurvy, leukæmias, etc. Trauma as from a fractured rib or gun-shot wounds, is another cause. Blood is sometimes expectorated in cases of high blood pressure, arteriosclerosis and emphysema.

In hæmoptysis, the blood is coughed up; it is frothy, bright red in colour, and is alkaline in reaction. After the actual attack, the sputum is streaked with blood for days together.

Treatment. Absolute rest in bed in the recumbent position is imperative. Food and stimulants should not be allowed. Morphia $\frac{1}{4}$ gr. may be injected hypodermically to calm the patient. If the focus of bleeding is detected in one of the lungs, an ice bag may be applied over it. In such cases, the patient should be inclined to that side as this will prevent the blood from being aspirated into the healthy lung. If the hæmoptysis is severe, the affected lung should be collapsed by an artificial

pneumothorax (for details of the technique of artificial pneumothorax see page 960). Other measures such as the inhalation of amyl nitrite 5 min., the injections of hæmostatic sera (Hæmoplastin) 2 c.cm., or the daily injection of emetine hydrochloride 1 gr. intramuscularly for 5 or 6 days may also be tried to control the hæmorrhage. Blood pressure should always be lowered by saline purges. Cardiac depressants such as aconite, are useful. Intravenous injection of a 10 per cent. solution of calcium chloride in 2 to 5 c.cm. doses, is often effective in these cases. Alcohol, tobacco and other stimulants should be forbidden. A mixture containing turpentine oil 10 min., tincture of squill 10 min., syrup $\frac{1}{2}$ dr. and cinnamon water to 1 oz., one dose thrice daily, is sometimes helpful. A solution of congo-red has been used in the treatment of hæmoptysis and is found to be a reliable hæmostatic. It is given as an intravenous injection, the usual adult dose is 10 min. of a 1 per cent. solution. This is often followed by a rigor of short duration. If there is recurrence of the hæmorrhage after the first dose, a further 10 min. dose may be given after four to six hours.

HÆMORRHOIDS OR PILES. These constitute a varicose condition of the veins of the anal canal and the lower inch or two of the rectum. Their characteristic course, situation in the loose areolar tissue and dependent position at the lowest part of the portal area with absence of valves, predispose to the condition and any pressure or obstruction in the portal or systemic circulation is reflected to the most dependent part where anastomosis of vessels occurs. They form a series of oval purplish swellings from which blood is readily expressed on pressure and hence piles are rarely detected on digital examination per rectum.

Piles are met with at all ages and in all conditions of life. They are common in young people with sedentary habits and are also common in elderly individuals especially with an enlarged prostate. Malignant diseases of the rectum often lead to piles. Pregnant women or women with pelvic and uterine tumours or displacements are also predisposed to this condition. Other ætiological factors are chronic constipation associated with a sedentary life, overuse of purgatives, a loaded rectum and obstruction to the portal circulation as from cirrhosis of the liver. Clinically piles are divided into external or internal. The external piles are situated at the anal margin and are covered with skin. Internal piles are situated above the anal canal and form a series of purplish ovoid bulges in the lower rectum. In the absence of complications, piles very seldom present symptoms beyond a little pruritus, some irritation and a sense of fullness at the anus immediately before and after defæcation. Hæmorrhage, inflammation, suppuration, thrombosis, prolapse and strangulation are the common complications of piles.

TREATMENT. (1) *External piles.* In all cases, the cause, if discovered, should be removed when possible. The regular use of a suitable laxative may prevent the condition. The anal region should always

be kept clean and all sources of external irritation removed. Where the piles are inflamed and thrombosed, absolute rest in bed, fomentations and warm enemata are indicated. If necessary the thrombosed mass may be incised and the clot removed, thus relieving the tension.

(2) *Internal piles.* As in external piles, the primary cause and all possible sources of venous congestion should be removed, the bowels should be regulated with mild aperients like confections of senna and sulphur, liquid paraffin, etc. The anus should be washed with cold water after defæcation and it is desirable for the patient to rest for some time after the act. If bleeding is severe, astringent suppositories or ointments of adrenalin, hamamelis, tannic or gallic acid should be used, for moisture and pruritus, soothing ointments or powders are indicated.

Infection treatment In cases where there is no permanent prolapse of the piles, several injections of a solution of 10 per cent. carbolic acid in liquor hamamelidis or of quinine and urethane into the mucous membrane of the anal canal are of much benefit. The treatment aims at the clotting and ultimate fibrosis of the hæmorrhoidal mass. Radical treatment by surgical operations are indicated where the loss of blood from the piles is rendering the patient anæmic and interfering with his general health and if the prolapse and inflammation be frequent. On the other hand, operations are contraindicated when piles are secondary to some conditions that can never be cured or relieved.

HEADACHE. This is one of the commonest symptoms met with in medical practice, and the various conditions with which it is associated are numerous. Headache may be the first symptom calling attention to the existence of grave organic disease, and the correct diagnosis of the cause of this symptom is very important. Too often unfortunately, treatment of headache precedes a careful investigation as to its cause, and an increased risk may thereby be incurred by the patient through the delay in recognising the actual cause.

The explanation of the mode of production of the pain known as headache is not easy, as the brain substance itself is insensible to mechanical stimulation. The membranes or at least the dura mater is on the other hand, sensitive, the arachnoid contains no nerves and the pia mater receives only sympathetic twigs for its blood vessels, but the dura is supplied with a large number of sensory fibre which leave the three divisions of the trigeminal nerve distant to the Gasserian ganglion and pass to the membrane as recurrent meningeal branches. The most important of these are the anterior and posterior ethmoidal and the tentorial nerves from the ophthalmic division and the recurrent branch from the mandibular division that re-enters the skull through the foramen spinosum. A recurrent branch from each vagus also contributes to the supply of the dura of the posterior fossa.

There can be no doubt that these dural branches are concerned in the production of headaches after the extirpation or injury after

herpes of the Gasserian ganglion the headaches rarely or never occur on the same side of the head. It might be assumed that all headaches are not due to irritation of the dural nerves, but it is obvious that pain can be felt only through the mediation of the nerves and these are the only sensory filaments that are distributed to the intracranial cavity. The dural nerves may be stimulated in many different ways:—

(1) By a rise of pressure within the skull, *e.g.*, by cerebral tumours and abscesses, meningitis and congestion of the cerebral vessels. (2) By poisons and toxins circulating in the blood, *e.g.*, alcohol, nicotine, toxins of the infectious fevers, nephritis, etc. (3) It may be a referred pain, *e.g.*, in disease of any visceral organ pain may be referred to a corresponding area on the surface of the body causing a state of abnormal excitability of that portion of the grey matter of the cord in which the visceral afferent fibres terminate (Ross, Mackenzie and Head). Disease in the distribution of the trigeminal nerve may excite pain that is referred to the head. Similar are the headaches of eye strain, and that associated with diseases of the nose and accessory sinuses. Head has also shown that local headaches may be the result of pain referred from one of the thoracic or abdominal viscera, due to the close central connection of the afferent fibres of the vagus with the central root of the trigeminal.

The following points are to be noted whilst investigating a case of headache: (1) Its position, whether general or circumscribed, the position of greatest intensity and whether it is superficial or deep in the head. (2) The time of the day in which it occurs or becomes more severe, whether it is constant or variable, and if it is liable to occur at more or less regular intervals. (3) The nature of the pain, whether it is a feeling of a pressure or a deep boring pain, a constant dull aching or a throbbing pain, an intermittent shooting pain or a feeling of the bursting of the head. (4) Exciting or aggravating causes, what it is that starts the headache and whether it becomes worse on lying down or walking about, when quiet or under excitement, and if food, exposure to cold, worry, or work, has any influence on it. (5) Conditions associated with the headache should be carefully investigated as they frequently throw light on its origin, *e.g.*, presence of vomiting or gastric disturbances, vasomotor or cardiac symptoms, the mental state during the attack, if the scalp becomes tender during or after the headache or whether it is accompanied by vertigo or ocular symptoms.

Though it might not be possible to include all the headaches in the categories suggested, the following classifications will be of practical value.

MIGRAINE. Most of the familial and constitutional headaches are migranous (see page 1410).

HEADACHES FROM RAISED INTRACRANIAL PRESSURE. The most important causes are tumours and abscesses of the brain, meningitis and cerebral

syphilis. Headache is not infrequently due to high blood pressure, especially when associated with arteriosclerosis.

The headache associated with cerebral tumour is generally described as a dull, deep-seated pain; sometimes the patient gets an intense throbbing pain or a feeling that the skull would burst open, from its severity. As a rule it is general but is often most severe in the frontal region or behind the eyes; occasionally it is worse in the occipital region, especially when the tumour lies in the posterior fossa, and then the pain frequently radiates down the back of the neck. The pain is more or less constant though severe exacerbations may occur, but many patients are free for considerable periods. An important feature is that it is usually most severe at night. If the intracranial pressure be very high, vomiting is generally associated with severer bouts of pain. The presence of papilloedema and symptoms of progressive cerebral disease are important signs in diagnosis.

In acute meningitis the headache is usually general but more intense in the occipital region. It is accompanied by stiffness of the neck and is aggravated by every movement of the head on the vertebral column and by pressure on the suboccipital region as these increase intracranial tension by compressing the distended posterior arachnoid cistern.

Headache due to syphilitic involvement of the brain may either occur soon after infection or be associated with the later manifestation of the disease. In early syphilis the pain is more or less constant and spreads from the occiput to the vertex or forehead and is particularly severe when the patient lies down or lowers his head. It may be a result of toxins reaching the brain as the infection becomes generalised, but is more probably caused by the early vascular and meningeal changes that often occur at this stage. Headache in the later stages of syphilis may be due to meningitis, infiltrations or cerebral vascular disease. Cerebral vascular diseases and arterial hypertension often give rise to headache. The arterio-sclerotic variety occurs in the fifth and sixth decades of life, in men more frequently than in women and usually on those who have led active and vigorous lives. It is associated with premature senility, mental deterioration and vertigo, and frequently insomnia or disturbed sleep at night with drowsiness during the day. The headache that is increased by mental and physical exertion, by worry and by bad ventilation is generally constant but never severe. The state of the retinal vessels by ophthalmoscopy gives valuable confirmatory evidence regarding the state of the vessels of the brain.

Treatment. The treatment should be directed towards the removal or alleviation of the cause. In cerebral arteriosclerosis the patient's mode of life must be carefully regulated, diet should be light, constipation avoided and alcohol limited or prohibited. The patient is always invariably better in the open air, and country life is consequently

advisable. A moderate amount of regulated exercise is usually advantageous. Iodide with bromides are usually the most effective drugs, nitrites in alkaline mixture are also frequently of value.

VASOMOTOR HEADACHES. Vaso-motor disturbances are frequently assumed to be causes of headache. There is some evidence that migraine is due to a periodic vasomotor upset, and headaches associated with disorders of the ductless glands and with certain physiological processes, such as menstruation, may be of this nature. Headache following prolonged physical and mental work, and epileptic seizures, are probably due to disturbances of the cerebral circulation. Another common cause of headache of this nature is paroxysmal cough, which raises the venous pressure producing venous congestion of the brain. The distressing headaches that sometimes occur in phthisis, bronchitis and asthma, are directly due to this cause. A rare variety, of sudden onset occurring in persons subject to angioneurotic oedema is probably due to patches of oedematous infiltration of the brain and meninges.

Treatment. The treatment of headaches due to circulatory disturbances is usually easy and effective. Cough must be checked by appropriate means, and overexertion must be avoided where this is the cause. When true vasomotor disturbances are responsible preparations of the ductless glands should be tried. Belladonna combined with bromides are also of value.

TOXIC HEADACHES. These may be due to exogenous poisons such as alcohol, nicotine, carbon monoxide, and lead, or to toxins manufactured within the body, those developed in the specific fevers, pneumonia, influenza, and those produced by gastro-intestinal disorders and in nephritis. The headaches that are so common in chlorosis are also of toxic origin. In fact, most poisons circulating in the blood cause headache, probably by their irritant action on the meningeal nerves.

The character and the situation of the pain depend upon the severity and nature of the intoxication. It is usually vertical or diffuse and of an intense bursting or boring character in acute infections and a more or less constant dull aching in chronic poisoning.

Treatment. In acute intoxications treatment can be rarely more than symptomatic. Rest preferably in a dark room, with cold application to the head and forehead and the administration of such drugs as antipyrin, phenacetin, caffeine and aspirin generally give some relief. In the more chronic cases one should always try to remove the cause. The importance of gastro-intestinal intoxication must never be forgotten, occasionally a purgative alone is sufficient but more radical and systematic treatment is usually required. The regulation of the diet and the use of liquid paraffin are usually effective remedies.

REFERRED HEADACHES. Defective eyes are certainly the most important source of this form of headache. The pain is usually bilateral and either frontal or temporal. It is seldom present or severe in the

morning. Diseases of the ear, especially when the middle ear is involved often give rise to pain which almost always spreads to the parietal and vertical regions and is often accompanied by tenderness on the scalp. Referred headaches of nasal origin are most commonly due to hypertrophy of the turbinates or deviation of the septum so that they press against one another. But headaches may also result from the absorption of toxic products when drainage is imperfect, and from inflammatory diseases of the nasal sinuses.

Treatment. The treatment consists in treating the primary causes only.

HEAT-STROKE (See page 218). This appears to be due to an auto-intoxication caused by lack of escape of heat from the body owing to insufficient evaporation from the skin and to the effects of muscular fatigue. As a result, toxic substances accumulate which have a selective action on the nerve cells. There is also deficient oxygenation of the blood. Some believe the condition to be a tissue acidosis, there being a retention of carbonic and lactic acids and a consequent depleting of the blood of its alkali content. In any case there can be no doubt that high relative humidity of the air is a very potent factor in producing attacks of heat-stroke and prostration as it notably checks cutaneous evaporation. Alcoholism is one of the chief predisposing causes. The milder forms are known as heat-exhaustion and heat-prostration; the severe form is sometimes associated with, and so far as pathology is concerned, may indeed be identical with, sun-stroke, in which there is a direct action of the solar rays.

Heat-stroke proper is a much more serious matter, and two clinical types may be differentiated: (1) thermic fever, (2) heat-cramp. An early warning sign in heat-stroke is a desire for frequent micturition and other prodromata are dryness of the skin, drowsiness, vertigo, headache and intolerance of light. The pulse is quick, rapidly becoming irregular, the skin is hot and dry and the temperature elevated. Delirium, coma or convulsions may ensue. The attack may come on very suddenly. Three main types have been observed:—(a) Asphyxial, where the soldier, fighting against an overpowering feeling of prostration, continues to march with tottering gait, fixed stare, contracted pupils and cyanosed face until he collapses senseless and apparently dead. His breathing is in abeyance, his pulse imperceptible at the wrist and his face deeply cyanosed. (b) Paralytic, in which there is deep coma, recurring convulsions, vomiting, diarrhoea and hyperpyrexia. The skin and ejecta may emit a mousey odour. (c) Psychopathic, which is not so deadly and in which the patient's mental balance is upset. His mind may be merely confused or he may pass into a muttering delirium or become violent and excited, or harbour delusions which may drive him to suicide.

Heat-cramp is chiefly seen amongst ships' firemen in the tropics and need not be further considered here. True heat-stroke must not be mistaken for an attack of cerebral malaria, though it is often very difficult to distinguish between them. The blood should be examined for parasites, the splenic region palpated and percussed, and the history if possible, obtained. Cerebral hæmorrhage in which the rise of temperature follows the insensibility, and cerebro-spinal fever have been mistaken for heat-stroke.

PROPHYLAXIS. Alcohol must not be taken at least during the day, the skin should be kept clean, the clothes should be loose and easy and the head, especially the occiput and the nape of the neck, well protected. Dark or tinted glasses protect the eyes from glare and the action of actinic or light rays.

TREATMENT. The milder degrees of sun headache are benefited by doses of caffeine and antipyrin or caffeine and phenacetin. For heat prostration get the patient into the shade, in a cool place if possible, lay him on his back, loosen his clothing especially about the neck, and massage his limbs. If there is collapse give ammonia or camphor and restore his bodily heat by hot applications. A warm bath may do good.

The special treatment for the asphyxial type of heat-stroke is artificial respiration, prolonged if necessary for a couple of hours. The paralytic type also requires prompt and vigorous treatment. The indications are to reduce the temperature, to get rid of toxic substances and to prevent cardiac failure. A simple means of reducing pyrexia is the cold abdominal pack. Where ice can be got it must be used to bring down the temperature, an iced bath or ice pack or rubbing the body with lumps of ice. A handy way is to lay the patient naked on a slightly inclined stretcher, pack him with ice and play a stream of iced water on his head from a distance of 15 to 20 inches. This ice-cold stream must not be continued for more than one or two minutes and collapse must be guarded against. Hence the rectal temperature must be taken and the cold applications stopped when the thermometer registers 102°F. Thereafter wrap the patient in blankets and apply hot bottles to the trunk and limbs. An ice-bag may be applied to the head. If perspiration sets in the prognosis is good. If the temperature rises again the cold applications must be resumed. Where ice cannot be got, a sheet soaked in water or dilute alcohol over which a draught of air plays, may be tried or cold water enemata given. There seems to be an advantage in making these alkaline, *i.e.*, give 1½ pints of a solution containing 2 per cent. sodium chloride and 2 per cent. sodium bicarbonate. All patients with a temperature of 103°F. or over should be placed at once in a bath of water, the level of which is high enough to cover the body except the head, which may be supported in a hammock or sling containing ice. Vigorous friction should be applied to the entire body by several persons, ice added freely to the water and the rectal temperature taken every minute. When the temperature falls to 102°F.

remove the patient from the bath and wrap in sheets or blankets, proceeding as above. Cardiac stimulants, especially caffeine and strophanthus should be freely given. A rectal enema containing 1 drachm of chloral hydrate has been found useful in quieting wildly delirious patients. Scopolamine, morphine and the bromides are useful in controlling restlessness and convulsions.

As there may be tissue acidosis slow intravenous transfusion of about 1½ pints of a 1 or 2 per cent. solution of sodium bicarbonate is indicated when the patient does not quickly respond to the treatment by cold. Such cases tend to develop oedema of the lungs and brain, hence before the transfusion, venesection should be practised as this will also help to eliminate toxic products. Normal saline may also be given intravenously after the bleeding. Recent work shows that certain cases of severe heat-stroke are markedly benefited by lumbar puncture, and the withdrawal of 20 c. cm. or more of cerebro-spinal fluid. It is probable that this operation will be more generally practised than heretofore, especially in cases classed as true sun-stroke.

Stimulants are often required, but strychnine is contra-indicated owing to its tendency to cause convulsions. When the latter occur give cautious inhalations of chloroform, watching the heart. Calomel and salines are indicated at a later period. Treat the psychopathic form as for heat prostration and on general principles.

COMPARISON OF THE ESSENTIAL FEATURES OF THE DIFFERENT DISORDERS
DUE TO HEAT

<i>Condition</i>	<i>Pathological changes</i>	<i>Clinical features</i>	<i>Treatment</i>
Heat cramps	Loss of sodium chloride.	Cramps	Salt and water by mouth. Hypotonic saline intravenously.
Heat exhaustion and heat prostration.	Circulatory failure from deficient blood supply.	Fainting, prostration, collapse, skin cool and moist, blood pressure low, temperature subnormal or elevated, pulse soft and small.	Fluids especially normal saline intravenously. General treatment for collapse.
Heat hyperpyrexia.	Failure of sweating.	Delirium, convulsion and coma. Skin dry and hot. Temperature 100° F. or more. Pulse rapid and full.	Cold water spray and fan.

HELMINTHIASIS. See page 254.

FILARIASIS. *Wuchereria bancrofti* infection (see page 335). Owing to the low-grade toxin of this parasite there may be no signs or symptoms in an infected individual for a long period. In susceptible individuals, however, there may be periodical anaphylactic symptoms like urticaria, headache, low fever, etc. At this stage the parasite is active and embryos are invariably present in the blood stream. There is moderate eosinophilia and complement-fixation test with *Dirofilaria immitis* antigen is positive.

According to the intensity of infection in an endemic area, various filarial diseases develop in the infected individual, viz., elephantiasis of limbs, breasts or genitals; chylocele, lymph-varix or chyluria. Hydrocele due to filarial infection is common in endemic areas. Lymphangitis of the extremities or of the abdominal region, orchitis, epididymitis or funiculitis recurring periodically is a common manifestation of filarial infection. When the worm dies in a lymphatic vessel or gland it is eliminated by abscess formation or it may become calcified or be absorbed.

Diagnosis. (1) Examine the blood for microfilariae. The method of examination of blood is to take 20 drops of peripheral blood at midnight in 10 c.cm. of 2 per cent. acetic acid solution. The blood is centrifuged and the deposit examined for embryos. In chyluria, examine the centrifuged deposit of urine for embryos; and in lymph-varix or lymph-scrotum examine the exudate or aspirated lymph for their presence. It is a general rule that the embryos are present in the blood in the early stages of the infection before the obstruction of lymphatics is complete. But in cases of chyluria they are invariably present in the blood as the block is near the juxta-aortic region where, owing to free anastomosis of lymphatics, they are able to reach the blood circulation. (2) Examine the blood for eosinophilia. Moderate eosinophilia of about 5 to 15 per cent. (total 500 to 1500 per c.cm. eosinophiles) is seen in early cases. In cases of lymphatic obstruction there may be no eosinophilia, but on the other hand, there may be leucocytosis of polymorphonuclear type during an acute attack. (3) Complement-fixation test with the *Dirofilaria immitis* antigen. A positive reaction indicates the presence of toxin of the parasite. In cases of lymphatic obstruction and where the lymphangitis is due to secondary organisms the test is negative. (4) Dermal test with the *Dirofilaria immitis* antigen. A positive reaction is indicative of filarial infection.

TREATMENT. The treatment of filarial infection, therefore, depends upon whether the infection is active or dead. It will be possible to classify the patients as toxic or septic types by the above procedure. In the case of the former, preparations of arsenic or antimony give beneficial results. In the case of the latter type, a thorough examination of the patient with a view to detecting any focus of secondary infection has to be made. The sites of secondary infections are septic gums, carious teeth,

tonsils, septic sinuses, bowel lesions or skin infections. Eradicate the focus or foci; immunise the patient with auto-vaccine wherever possible. Stock filarial mixed vaccines consist of streptococci 100 millions and staphylococcus albus and aureus each 500 millions per c.cm. the dose commencing from 0.1 c.cm. generally increased to 1 c.cm. and a course of 10 or more injections has always been found to be very beneficial. Mixed types need combined treatment.

The routine course of treatment followed: 1. *Filarial lymphangitis, lymph-adenitis, orchitis and funiculitis.* Rest in bed, calamine lotion applied locally and diaphoretics and hydrotherapy for fever. For prevention of recurrence of acute attacks treat the case according to whether it is the toxic or septic type. 2. *Filarial abscess.* Hot boric compresses and surgical treatment by evacuation and aseptic dressings. A course of antovaccine, wherever possible, is recommended. 3. *Lymph-scrotum, lymph-varix and hydrocele.* Treatment is chiefly surgical. Palliative treatment consists in the application of suspensory or pressure bandages. 4. *Elephantiasis.* (a) Elimination of septic focus. (b) Vaccine and non-specific protein therapy. (c) Elastic pressure bandage. (d) Surgical treatment (Kondoleon's operation, etc.). 5. *Chyluria.* Compounds of arsenic or antimony (e.g., tryparsamide, founadin and neostibosan) have given good results in relieving this affection. Since there is generally a secondary infection in cases of chyluria 'midstream' urine or a catheter specimen culture and a course of autovaccine is to be recommended. Rest in bed and restriction of fats and fluids during treatment are helpful. Liquid extract of Hamamelidis (B. P.) and Liquid extract of Lodh are sometimes effective in dram doses orally.

GUINEA-WORM INFECTION. *Dracunculus medinensis.* (See page 333). This is very local in its incidence, the infection is endemic in several areas in North-West Frontier Province, the Punjab, Rajputana, Central Provinces, Bombay and Madras Presidencies. It is essentially an infection of the areas in which there is water scarcity and where the supply of water is obtained from step-wells or tanks, etc. The adult female usually appears on the lower extremity where it causes a blister; when the blister opens the uterus protrudes and discharges embryos every time it comes in contact with water. The embryos develop inside the hæmocele cavity of cyclops and undergo development. They become infective in 2 to 4 weeks. When the infected cyclops are swallowed by man with drinking water the hydrochloric acid in the stomach kills the cyclops but the larvæ become active and piercing the dead cyclops escape and enter the tissue. They reach maturity in about one year.

Anaphylactic symptoms like articular, giddiness, and vomiting, etc., are complained of just before the production of the blister. The adult worm during its migration may die and get calcified if it is not able to reach the skin surface. Such calcified worms produce rheumatic pains, synovitis or periostitis when it is desirable to remove them. They can be easily detected by X-rays. Secondary infection with streptococci or

staphylococci is very common in this infection. If the worm breaks in the process of extraction acute cellulitis may result due to streptococcal infection.

Diagnosis. Generally the diagnosis of guinea-worm infection is easy. In difficult cases the following points are of help. (1) Knowledge of distribution of guinea-worm infection. (2) History of previous appearance of worms. (3) Moderate eosinophilia 10 to 15 per cent. (1000 to 1500 per c.cm.). (4) Positive complement-fixation test. (5) Positive dermal test with *Dirofilaria immitis* antigen.

Treatment. Anaphylactic symptoms are relieved by the injection of liq. adrenalin hydrochloride $\frac{1}{4}$ c.cm. intramuscularly. Repeated pouring of cold water over the worm will hasten the discharge of the embryos, but it takes 2 to 3 weeks to empty the worm of its embryos by this method. Ethyl chloride spray hastens and empties the worm in less time. Gentle traction and winding the worm on a match-stick day by day is an ancient method of treatment. Injections of 1 or 2 c. cm. of chinosol solution 1 in 400 or acriflavine 1 in 100 into the body of the worm or into the subcutaneous tissue will kill the worm and it may be easily extracted in a day or two. Injection of tartar emetic intravenously, reported by Macfie to kill the adult worm, has not been confirmed.

Prophylaxis. Prevention of this infection is simple. Filter drinking water through coarse muslin. Step wells and tanks are the source of infection. Surrounding the wells with a parapet and the introduction of pumps for drawing water will prevent the spread of the infection. Various measures for destroying the cyclops such as heating well-water by steam or the addition of caustic potash, permanganate of potash or bleaching powder have been recommended but they are expensive as they would have to be done periodically.

INTESTINAL WORMS (see page 266). *Diagnosis of helminth infections in stools.* A supply of saturated salt solution must be prepared. To be certain it is of sufficiently high specific gravity, excess of salt is placed in a vessel containing water and put over the fire where it is allowed to boil gently until a scum forms on the surface of the water. When this occurs it can be allowed to cool and it is placed in a bottle where it will last indefinitely.

Take a small receptacle (a tin pill box or *dibia* is one of the best) with a capacity of about 20 c. cm. Place about 1 c. cm. of stool in the tin and add a few drops of salt solution. Stir thoroughly with a glass rod or piece of stick until the stool is completely emulsified into a smooth paste. This thorough breaking up of the stool is the essential step in the method if it is to be successful. Add more salt solution slowly, stirring meanwhile, until the tin is nearly full, and then add more salt solution drop by drop until the fluid is just level with the top of the tin. Place a microscope slide over the top of the tin, and if it has been correctly filled almost the whole of the slide within the borders of the tin is in contact with the fluid but none has run down the sides. Allow this

to stand for twenty minutes and lift the slide steadily, taking care to keep it horizontal and then turn it over. Examine with the ordinary low power and the eggs will be found floating on the surface of the fluid on the slide. It is not necessary but it is preferable to use slides 2" x 3" rather than the ordinary 1" x 3" slides as the former completely covers the opening of the tin with a wide dry border all round, and hence holds the fluid better than the narrow slide, when it is being turned over. The eggs found by this method are hook-worm, ascaris, trichuris, *trichostrongylus*, *enterobius*, *strongyloides* (occasionally), *hymenolepis nana*, and *hymenolepis diminuta*.

EGGS THAT FLOAT IN SATURATED SALT SOLUTION

(By salt flotation method)

	Appearance, colour, etc.	Size.	Measurement in microns.
<i>Ancylostoma duodenale</i> .			
<i>Necator americanus</i> .			
<i>Ancylostoma braziliense</i> . (hookworms).	Colourless.	Medium	70-60 x 35-40
<i>Ascaris lumbricoides</i> (roundworm).	Brown, knobly.	Large	70-50 x 50-40
<i>Trichuris trichiura</i> (whipworm).	Dark brown, knobbed at each end.	Small	55-50 x 25-20
<i>Trichostrongylus</i> (similar to hook- worm, rare, and does not cause symptoms).	Colourless.	Medium	95-75 x 45-35
<i>Enterobius vermicu- laris</i> (threadworm).	Colourless, with tadpole larva.	Small	60-50 x 30-20
<i>Heterodera radicola</i> (not true parasites, accidental).	Colourless.	Large	100 x 45
<i>Strongyloides stercor- alis</i> (rare, larvae in stool).	Colourless.	Medium	50 x 30
<i>Hymenolepis nana</i> .	Colourless. Onchosphere with fila- ments.	Small	45-30. (Oncho- sphere 19-16).
<i>Hymenolepis diminuta</i> .	Brownish, no filament.	Large	85-60. (Oncho- sphere 36-18).

The eggs that do not float in saturated salt solution are unfertilised ascaris, *tænia saginata*, *tænia solium*, and all fluke eggs.

EGGS THAT DO NOT FLOAT IN SATURATED SALT SOLUTION

	<i>Appearance, colour, etc.</i>	<i>Size.</i>	<i>Measurement in microns.</i>
<i>Ascaris lumbricoides</i> (unfertilized).	Brown, knobbed. Yolk granules.	Large	80 × 40
<i>Tænia saginata</i> (beef tapeworm).	Dark brown, 3 pairs of hooks.	Small	40-30 × 30-20
<i>Tænia solium</i> (pork tapeworm).	(Indistinguish- able from the last)		
All trematodes, e.g., <i>Fasciolopsis buski</i> .	Light brown with oper- culum.	Large	140-130 × 85-80

TREATMENT. HOOKWORM. (1) *Oil of chenopodium*. This form of treatment is employed when carbon tetrachloride is contraindicated. One gelatine capsule containing 10 min. of oil of chenopodium is given each hour for three doses and this is followed by a purgative two hours after the last dose (see page 298). (2) *Carbon tetrachloride*. Only chemically pure samples must be used. It is administered in a dose of 48 min., well shaken up in 2 oz. of haustus magnesium sulphate (see page 284). (3) *Oil of chenopodium and carbon tetrachloride*. The combined treatment is of use, because it gets rid of more hookworms than either drug alone and the oil also acts on any ascaris that may be present. The dose is 15 min. of oil of chenopodium and 45 min. of carbon tetrachloride, thoroughly shaken up in 2 oz. of haustus magnesium sulphate immediately before administration. (4) *Oil of chenopodium and tetrachlorethylene*. The latter drug is not so toxic as carbon tetrachloride and it can be given in doses of 1 dr. shaken up in magnesium sulphate solution with 15 min. of oil of chenopodium in the same way as carbon tetrachloride.

For children. In the case of oil of chenopodium 1 min. for each year of age is given up to the age of sixteen and in the case of the other drugs the usual formula (age divided by, age + 12) may be employed.

ASCARIS. *Santonin and oil of chenopodium*. In uncomplicated ascaris infection, 3 gr. of santonin and 15 min. of oil of chenopodium are used. The oil of chenopodium is placed in a hard gelatin capsule and swallowed at the same time as the santonin, with a draught of water, followed in two hours by a dose of haustus magnesium sulphate (see page 310).

*TAPEWORM (see page 271). The best treatment for this is carbon tetrachloride alone.

THREADWORM OR OXYURIS. *Enterobius vermicularis*. Carbon tetrachloride in the dose employed for hookworm infection has been found

to be the most effective drug. The worms are difficult to eradicate, and combined with drug treatment precautions should be taken to prevent re-infection by carrying eggs from the anus to the mouth on the fingers. The region of the anus should be smeared every night with dilute ammoniated mercury ointment (5 gr. to 1 oz.). This serves the double purpose of relieving the pruritus and killing the female worms which wander out of the anus at night. Gloves which are washed every day may also be worn all night. If this routine is persisted in a cure is usually effected.

WHIPWORM (*Trichuris*). No cure is effective; but the worms rarely cause symptoms.

STRONGYLOIDES. Gentian violet in doses of 1 gr. three times daily for three days is sometimes efficacious.

FASCIOLOPSIS BUSKI (see page 331). This is the only fluke infection in human beings in India and it is not common. Carbon tetrachloride in the dose employed for hookworm is a sure cure.

Other anthelmintic treatments have proved relatively ineffective in spite of the reports of their success in other parts of the world. Among these may be mentioned gentian violet for strongyloides and trichuris, hexylresorcinol, a drug recently strongly recommended has been tried but has not been found nearly as good as existing treatments.

General instructions. The only purgative employed in anthelmintic treatment of any kind is the magnesium sulphate mixture.

All patients are given a light meal the evening before treatment, the treatment is given the first thing in the morning, and no food is allowed until the bowels have acted freely at least on one occasion.

None of the above anthelmintic treatments should be repeated in less than ten days, on account of the possibility of cumulative effects of the drugs.

HEPATIC ABSCESS. See page 374.

HEPATOMEGALY. The liver is the largest gland in the body. Its normal weight varies between 45 to 60 oz. It is composed of numerous lobules which may be diagrammatically considered as made up of a series of radiating tubular glands with the closed ends towards the central hepatic vein. The polygonal glandular cells lie along the walls of the tubular glands. Their lumens constitute the bile capillaries which open into the bile duct. Between the tubular glands run the wide portal vascular capillaries passing from the portal tract to join the branch of the hepatic vein in the centre of the lobule. Along the walls of these capillaries lie a number of endothelial cells known as Kupffer's cells. Each portal tract contains a branch of the hepatic artery, vein and biliary duct.

The main functions of the liver may be broadly defined as arresting, storing, modifying or transforming all substances brought to the

liver by the portal vein. The various functions are briefly reviewed as follows: (1) Secretion of bile, which helps digestion especially of fat. (2) Glycogenic function; glucose is absorbed, some of it is utilised at once while the excess is arrested by the liver, dehydrated and converted into a colloid substance known as glycogen. It can be again hydrated and changed back into glucose according to the necessity. This is done by the ferment amylase, which is present in normal hepatic cells. (3) Protein metabolic function, *i.e.*, production of urea, uric acid and creatinin. (4) Hæmopoietic function (a) it acts as a storage of iron, (b) it acts as a blood-forming organ especially in foetal life, and (c) it manufactures fibrinogen. (5) Protective function, *i.e.*, the power of detoxicating the poisonous substances absorbed from the alimentary canal.

Both the liver and the spleen become considerably enlarged in bacterial and protozoal infections and intoxications. Various causes of hepatomegaly are: malaria, kala-azar, leukæmia, cirrhosis (portal and biliary), venous congestion as in heart failure, tropical liver (this vague term has been applied to the hyperæmic condition of the liver occurring in warm climates; it is really due to over-indulgence in food and alcohol, accompanied by lack of exercise), amoebic hepatitis, abscess, syphilis, malignant tumour, hydatid cysts, splenic anæmia, Hodgkin's disease, rickets, cholangitis, bronzed diabetes, perihepatitis, degenerative changes *e.g.*, fatty and amyloid, relapsing fever, Weil's disease and trypanosomiasis.

For diagnosis and treatment of the tropical conditions of hepatomegaly the reader is referred to respective sections in the book.

HERPES. See page 1212.

HICCOUGH. This is a sudden clonic spasm of the diaphragm accompanied by a spasmodic closure of the glottis which produces the characteristic sound. In most cases it is transient and of little importance but it is of grave prognostic importance when it sets in as a complication during the course of a disease. The condition starts very early and may be seen in breast-fed babies and is probably due to overdistension of the stomach after feeds and swallowed air. Inflammation of or pressure on the phrenic nerve or a reflex through the vagus nerve often initiates the process in adults. It is a common symptom and an evil omen in many diseases, particularly, in general and local peritonitis, in acute intestinal obstruction, when tympanitis sets in as a complication in enteric fever and in the last stages of many chronic exhausting diseases such as tuberculosis diabetes, etc. It sometimes occurs after the ingestion of hot, irritant and spicy food. It may be excited reflexly by organic diseases of the nervous system such as meningitis, tumours of the brain and encephalitis. It is a common symptom in neurosis, hysteria, epilepsy and chorea. It is commonly seen in toxic states of pregnancy

such as hyperemesis gravidarum, eclampsia, etc., and it may complicate Grave's disease or Addison's disease. The condition also starts as a reflex cause in diseases of the pleura and pericardium. Besides all those that have been mentioned, there are the idopathic and epidemic cases.

Epidemic hiccough is a nervous form of hiccough and has been regarded as a form of encephalitis lethargica. The condition may persist without intermission for several days.

TREATMENT. In all cases attempts should be made to investigate and detect, if possible, the primary causes and when found, it should be properly dealt with. When hiccough persists, it is most distressing and troublesome to the patient and various measures have been tried to control it. In children a spoonful of hot water, weak solution of sodium bicarbonate or dilute lemon juice may help to control it. The most frequently employed household remedies in cases of mild attacks are pressure on the back of the neck, holding the breath, swallowing a bolus of food, tickling the nose to induce sneezing, gentle compression of the upper part of the thyroid cartilage, traction of the tongue, sipping cold drinks and swallowing small lumps of ice. A tumblerful of warm water containing bicarbonate of sodium 20 gr., flavoured with peppermint, may be tried in some cases. Applications of stimulating nature to the epigastrium such as warmth and small mustard plasters are occasionally useful. Sometimes faradism may be tried and a tight bandage or plaster around the upper part of the abdomen may give relief.

In intractable troublesome cases sedatives are indicated to afford rest to the patient and opiates, bromides, chloral, hyoscine and even apomorphine may be tried in such cases. Benzyl benzoate is highly spoken of in the treatment of persistent hiccough, 20 to 30 drops of a 20 per cent. alcoholic solution may be given with milk or water; 25 to 30 min. of ether injected intramuscularly has been found to give relief in a few cases.

Of other internal remedies, nitroglycerine in doses of 1/100 gr., has been found effective in some cases. Oil of turpentine in doses of 10 min., has been highly recommended by some. Liquid extract of ergot in 1 dr. doses frequently repeated, has been very successful in some cases. One minim doses of tincture of hyoscyamus, repeated every half hour, are said to yield good results in most cases. Musk 5 to 10 gr. in a pill with liquorice may also be tried.

Sopars advocates gastric lavage in persistent cases. Lichtenstein (1928) has obtained good results with a dilute cocaine-epinephrine solution containing a small amount of phenol applied to both nostrils on pledgets of cotton. The inhalation of carbon dioxide gas mixed with varying proportions of oxygen has given encouraging results. An ordinary paper bag of medium size is placed over the mouth and nose

and the patient is asked to breathe into it. By rebreathing the expired air, the concentration of carbon dioxide in the blood is raised.

In severe intractable cases of hiccough operation on the phrenic nerve has also been suggested.

HILL DIARRHŒA. See page 884.

HOARSENESS. Hoarseness or alteration in the voice of an individual may be physiological or pathological. The former is generally seen in subjects at puberty where a marked alteration or a sudden break in voice is noticed in the individual. The pathological causes are manifold and may be met with at any period of life from the cradle to the grave. It may be acute, of transient duration as in simple laryngitis or it might turn to a chronic form resulting in a permanent change in the quality of the voice. The causes may be briefly discussed as :—(1) *Congenital syphilis*. The hoarse cry of the new born is highly suspicious of inherited syphilis and other symptoms of the disease should be looked for. If the diagnosis is positive, anti-syphilitic treatment should be started at once. Inunction with mercury is a favourite old treatment of the syphilitic child. The child is debilitated, of low resisting powers and should be given nourishing food. The child is liable to pulmonary complications and hence should always be kept warm. A drastic antisymphilitic treatment is always indicated for the parents in such cases. (2) *Papillomata of the larynx*. The combined symptom of hoarseness and stridor in otherwise healthy children should arouse a strong suspicion of growths in the larynx. It might encroach on the glottic area and precipitate an emergent necessity of low tracheotomy. The condition is often confused with diphtheria. The growths require frequent surgical removal though recurrences are common. They are locally infective and hence do not permanently disappear till a sufficient degree of immunisation is established. (3) *Functional aphonia*. Like the breaking of voice at puberty in young males, this condition is most frequently met with in the female sex from puberty to the menopause. This is caused by paresis of the adductor muscles of the cords. It is seen in young healthy women though sometimes it follows a slight attack of tonsillitis, laryngitis, sudden physical or mental shock. The diagnosis is easy as when such a patient is asked to cough, the sound of the voice is produced in normal manner, that is the adductors for the moment come into close apposition. It can be cured by suggestion only. The relatives of the patient are sent away and the patient is assured that she would be cured with the medicine prescribed which would strengthen the weak muscles of the sound-box. As a rule, definite improvement has followed such treatment. Sometimes the application of a strong faradic current between the intra-laryngeal electrode and the external terminal over the larynx produces the desired effect.

(4) *Vascular fibroma of the vocal cord*. These are small peasized benign growths, sessile or pedunculated, found near the edge of the vocal cord. They are generally seen in adult males and interfere with the production of normal voice. The treatment is to remove the growth surgically and the patient is to be asked to whisper for at least a fortnight after such operation. (5) *Singers' nodules*. They are small white discrete projections found at the edges of the cord. The condition is generally met with in teachers or singers who use their voices at the maximum pitch. The treatment is to give a prolonged rest to the voice but the use of the galvanocautery may be necessary where the growths exceed the normal size. (6) *Chronic laryngitis*. Here the infection is spread from the neighbouring regions such as the nasopharynx and the accessory air-sinuses. It affects both the vocal cords and is seen in adults. The condition flares up in the presence of constitutional diseases such as syphilis, gout, rheumatism, diabetes, albuminuria, etc. The treatment should be directed to improving the neighbouring pathological condition and to curing the constitutional diseases, if any. (7) *Syphilitic laryngitis*. This condition is generally seen in the tertiary stage of the disease. Gummatus infiltration, ulceration, perichondritis, necrosis of bone or of the cartilage are the pathological changes met with in the course of the disease. Hoarseness results when the vocal cords are infiltrated or ulcerated by the breaking down of gummata. The treatment includes the administration of anti-syphilitic drugs to the patient. (8) *Tuberculous laryngitis*. It is always secondary to a primary lesion in the lungs. The patient is generally young and debilitated, and in addition to hoarseness of voice, complains of a slight cough. Clinically, the lesion consists of a nodule or an ulcer affecting the vocal cord. The ulcer might spread to the glottic region. General anti-tuberculous measures combined with prolonged vocal rest go a long way to improving the condition. If the pulmonary condition improves, a galvano puncture of the ulcer might facilitate a rapid healing fibrosis of the same. (9) *Cancer of the larynx*. Squamous-celled epithelioma is common in the larynx and is generally seen in males over forty years of age. It is the intrinsic variety of the malignant growth affecting the vocal cord that causes hoarseness at a very early stage of the disease. Diagnosis is made by laryngoscopy and time should never be lost till the movement of the cord is impaired during phonation. Treatment of an early epitheliomatous condition of the vocal cord is more hopeful. The most favoured operation is laryngofissure and its radical removal after it. On the other hand, the insertion of radium needles after a window resection operation promises a better chance of recovery of voice afterwards. (10) *Paralysis of cords*. Besides those that have already been dealt with, another causal factor of hoarseness is paralysis of one or both vocal cords due to a lesion of the recurrent laryngeal nerve. Such a lesion may be both central or peripheral. Paralysis

of the cord of a central origin is met with in progressive bulbar paralysis, basal pachymeningitis near the region of the jugular foramen, syringomyelia, disseminated cerebro-spinal sclerosis and in tabes. Radiograms often disclose factors responsible for peripheral lesions of the nerve resulting in unilateral paralysis of the cord. Treatment of such a condition aims at removing the factors or treating the diseases responsible for bringing about the change in the voice. Local treatment in form of sprays, paints and gargles of the neighbouring regions should also be adopted while carrying out the specific ones where needed.

INFECTIOUS DISEASES. *Isolation.* In undertaking the care of an infectious case the physician is responsible for the treatment of the patient and the protection of the community. Isolation is therefore the most obvious duty. This can be most satisfactorily attained in the local hospital particularly in cases of small-pox, cholera, cerebrospinal meningitis, diphtheria, etc. Diseases such as measles, mumps and chicken-pox may be treated at home. A good airy room should be chosen for the sick-room. An overall apron is used by the attendants and arrangements are made for scrupulous washing of hands in some suitable antiseptic solution (mercury perchloride lotion 1 in 2,000) on leaving the room. Domestic utensils should be set aside for the exclusive use of the patient and thoroughly disinfected before they are taken out of the room. All bed-linen and clothes should be soaked in 1 in 40 solution of carbolic acid before being sent to the laundry. In diseases like cholera and enteric fever, the excreta should be mixed with an equal amount of 1/20 carbolic acid and allowed to stand for an hour before being thrown into the drains.

Nursing. The patient should be sponged at least once a day, the whole body being washed with soap and warm water, limb by limb, and dried rapidly with light friction. If the temperature rises above 102.5°F., an ice-bag is applied to the head; if it rises above 103.5°F. a tepid or cold sponging may be given. The back and dependent parts should be rubbed every morning and evening with a little spirit and powder. Attention should be directed to the cleanliness of the mouth. All decaying matter and sordes should be carefully removed from the teeth and gums and the whole mouth cavity including the tongue should be cleaned at least twice a day, and in bad cases more often with a cotton wool swab. This should be followed by application of boroglycerine. It must be remembered also that a free supply of fluids helps to keep the mouth moist and comfortable and the patient should be encouraged to drink plenty of cold water.

Diet. A fluid diet, consisting chiefly of milk, is the most suitable to adopt (see page 1399).

Medicinal treatment. It depends on the nature of the disease, etc., and should consist of specific (if any) and symptomatic treatment.

INFECTIOUS DISEASES
INCUBATION, ISOLATION AND QUARANTINE PERIODS AND DAY OF
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Disease	Incubation period	Date of eruption	Isolation period
Cerebro-spinal fever	1 to 5 days	2nd day	Till the naso-pharyngeal swab is negative
Chicken-pox	10 to 21 days (generally 14 days)	1st day	Till all scabs have separated
Cholera	A few hours to 6 days		Till stools are free from bacilli
Dengue	4 to 7 days	Initial erythematous on 1st day. Morbilli form eruption on 4th or 5th day	
Diphtheria	2 days (1 to 5)		Until 3 consecutive culture reports are negative
Dysentery—bacillary	A few hours to 7 days		Till the stools are free from bacilli
Enteric fever	14 days (5 to 23)	7th day	Till excreta are free from bacilli
Influenza	A few hours to 3 days		For a few days after the acute symptoms have passed off
Measles	10 to 17 days	4th day	14 days
Mumps	2 to 3 weeks		3 weeks from onset of parotitis (1 week after the swelling subsides)
Plague	3 days (2 to 7)		4 weeks after the temperature is normal
Relapsing fever	5 to 10 days		Till the patient is well and deloused
Rubella (German measles)	15 to 18 days (10 to 21)	1st day	7 days from appearance of rash
Small-pox	12 days (8 to 16)	3rd day	Till all scabs have separated
Typhus fever	12 days (5 to 23)	5th day	4 to 5 weeks from commencement of illness
Whooping cough	7 days (5 to 21)		6 weeks (till no whoop for 2 weeks)

Quarantine period is usually 2 to 3 days longer than the maximum incubation period.

INFLUENZA. See page 983.

INSOMNIA. See page 223.

INTRAVENOUS THERAPY. See page 34.

INSECT STINGS. Mechanical removal of the venom by suction is impossible in the case of insect stings. Surgical procedures are rarely necessary, except in case of œdema of the glottis. In the case of the bee stings the removal of the sting is important. Another therapeutic measure is the neutralization of the toxins. This measure is based on the erroneous belief that formic acid is involved in the action of insect venom, but in spite of this, the frequently employed ammonia is not entirely ineffective. Other substances that formerly were thought to be neutralizing agents, such as sodium bicarbonate, lime water, magnesium oxide; are sometimes beneficial because they counteract the tension. Some measures are employed to make the venom insoluble. In this connection mention is made of one of the oldest remedies, namely, sodium chloride, which is dampened and applied or rubbed in. Other substances belonging to this group are magnesium sulphate, ammonium sulphate, some alcoholic preparations tannic acid, plant juices that contain tannin and certain heavy metals. The use of heat likewise produces coagulation of the venom. Frequently attempts are made to burn out insect stings. Tincture of iodine, compound solution of iodine chlorine water, surgical solution of chlorinated soda and similar preparations aim at a chemical destruction of the venom. Potassium permanganate likewise is much used. To counteract the pain, local anæsthetics may be employed and the itching may be counteracted by anti-inflammatory agents, such as the phenols and the volatile oils. As a prophylactic measure it is advisable to disinfect the wound with iodine, formaldehyde or a phenol preparation. Most fatalities which occur in connection with insect stings are the result of bacterial infections rather than of the insect venom. The general treatment varies in the different cases. Stings into the blood vessels may produce severe symptoms that resemble anaphylactic shock. To counteract allergic conditions, epinephrine and intravenous calcium therapy have been recommended.

JAUNDICE. The word *jaundice* is derived from the old French *jaunisse*—yellow. It represents a morbid condition due to increased amount of bile pigments in the plasma and tissues. It is characterised by varying grades of yellowness of the skin, mucous membranes, conjunctiva, fluids and tissues. The central nervous system, nerves and cartilages are the only tissues which do not absorb the pigment. The substance primarily involved in the production of jaundice is bilirubin, which is normally found in the blood serum and bile. The yellow colour of the tissue is due to the presence of this pigment.

Two methods of production of jaundice are recognised :—

(a) One is primarily due to an increased amount of serum bilirubin, *i.e.*, hyperbilirubinemia and is associated with a diminution in the bilirubin excretory ability of the liver. This type of jaundice is seen in diseases such as pernicious anæmia, myocardial insufficiency, hæmolytic jaundice, etc., where there is increased red blood cell destruction and probably a diminished excretory ability of the liver.

(b) The other is primarily due to discontinuity of the cells lining the bile canaliculi, thereby permitting the reabsorption into the lymph vessels and capillaries, of bile which has been excreted through the liver cells. In this manner, bilirubin, bile salts and cholesterol are increased in the blood serum. Associated with this there may be an increase of serum bilirubin which has not been excreted through the liver cells due to the damage done to these cells. Discontinuity of the cells of the bile canaliculi is caused by biliary obstruction. The back pressure and increased intrabiliary tension separate the cells and permit the absorption of bile into the lymph and blood. This can also be produced by toxins or infections destroying the liver cells. Such cases are associated with an increase of serum bilirubin which has not been excreted by the liver cells on account of the damage to these cells. Jaundice of this character need not be associated with the absence of bile in the stool.

Jaundice has been recently classified clinically by Arnold Rich into two main types : 1. *Retention jaundice*. In these cases there is an excessive production of bile pigments by the reticulo-endothelial cells and diminished excretion of bile by the liver cells. The latter is due to sub-normal function caused by various factors such as anoxæmia, febrile disease or immaturity of liver cells. The excess of bile pigments enters the general circulation. The causes of this group are (a) pernicious anæmia, sickle cell anæmia, paroxysmal hæmoglobinuria, mismatched transfusion, phenyl-hydrazine poisoning; (b) chronic passive congestion as a result of cardiac decompensation; (c) febrile diseases associated with anoxæmia resulting from hæmolytic septicæmias, malaria, blackwater fever; and (d) immaturity of liver cells in the new born. 2. *Regurgitation obstruction jaundice*. The bilirubin in the blood is not excreted normally either owing to necrosis of the liver cells or to obstruction of bile canaliculi or ducts. The ducts rupture and bile passes back into the blood channels. The main causes of this group are (a) toxic agents, chemical, vegetable, bacterial or undetermined as in cases of idiopathic acute yellow atrophy; (b) plugging, stricture or pressure of the biliary passage by calculi, inflammatory exudates, parasitic masses, neoplasms, or enlarged hepatic lymph nodes. A combined form of jaundice may also occur, in which there is an excessive production of bile pigments.

Rich holds that excessive production of bile pigments alone will not cause jaundice. An additional factor, namely, derangement of the liver

cells, which interferes with excretion, is required. Totally dissimilar clinical types of jaundice, such as toxic processes caused by chloroform and an obstructive process due to a calculus, are classed together by Rich as regurgitation jaundice.

Van den Bergh's test. It is often utilised to distinguish the different types of jaundice. He showed that when Ehrlich's diazo reagent was added directly to normal serum no unusual colour developed. When, however, the serum proteins were precipitated by alcohol the addition of the reagent to the supernatant fluid produced a lilac colour (indirect reaction) in a great number of cases. He further showed that when bilirubin was increased in the serum, this colour became intensified. He later on showed that in conditions of jaundice, produced by a flow of bile back into the blood stream, an immediate colour reaction (direct reaction) could be obtained by the addition of the reagent directly to the serum without the need of previously precipitating the proteins. The colour was produced by the formation of diazo-bilirubinate.

The explanation of the direct and indirect Van den Bergh reaction was finally given by Barron in the following manner. When bilirubin in small amounts is taken up in a watery solution, the addition of Ehrlich's diazo reagent will immediately cause the formation of violet, blue or pink colour depending upon the acidity or alkalinity of the solution. When a small amount of bilirubin is added to normal serum the addition of Ehrlich's reagent does not produce a prompt reaction. If, however, before the addition of the reagent a small amount of any surface-tension-reducing substance, such as bile salts, cholesterol, sodium oleate, etc., is added to the treated serum, the addition of Ehrlich's reagent will produce an immediate reaction. The addition of the surface-tension-reducing substance apparently splits off the bilirubin from its protein combination and the freed pigment, when brought into contact with the reagent, causes a prompt positive colour reaction.

Generally three types of Van den Bergh reaction are described.

1. *Indirect reaction.* No colour appears for at least 1 to 2 minutes after the addition of the reagent. Some colour may appear after this time, but not in maximum intensity. The major reaction occurs only after the precipitation of serum proteins.

2. *Direct reaction.* The colour appears at the time of addition of the reagent and reaches its maximum intensity in about 30 seconds.

3. *Biphasic reaction.* The colour appears at once at any time up to 30 seconds after mixture of the serum and reagent. The maximum intensity may occur at almost any reasonable time after this.

The interpretation of these reactions is as follows.

- (a). Jaundice produced by an accumulation of bilirubin in the blood serum in those cases in which there is no destruction of the bile canaliculi, is represented by the indirect Van den Bergh. Values as high as 20 mg. per 100 c.c. of serum have been reported in these

cases, although the usual finding is about 2 to 5 mg. It is interesting that although the tissues can remove the pigment from the blood, the kidneys are unable to do so and bilirubin is not found in the urine of these cases.

(b) Jaundice produced by an accumulation of bilirubin in the blood serum in those cases in which there is destruction of bile canaliculi as shown by the direct Van den Bergh and is found (according to Barron) in association with a substance which reduces the surface tension of the serum. In these cases there is a direct passage of bile from the liver into the circulation and bilirubin, bile salts and cholesterol increase in the blood serum.

(c) It is questionable if the biphasic reaction has any real significance as an entity. It may be better to place it in the group of direct reactions. The basis for this reasoning is as follows: any colour that appears within the first 30 seconds is reagent and non-absorbed bilirubin, *i.e.*, bilirubin not taken up by protein, and therefore, diagnostic of the presence of bile products which have passed through the liver and have been reabsorbed into the serum (discontinuity of bile canaliculi). The colour which appears after this time may represent bilirubin which has not passed through the liver or reabsorbed bilirubin which has been absorbed by serum proteins because of a lack of surface-tension-reducing substances.

When there is necrosis of the liver cells, the organ may become unable to excrete the normal amount of bilirubin. Furthermore, in such diseased conditions, there is often an overproduction of bilirubin from an increased destruction of red blood cells, and a stage is reached in which there is a marked increase in the indirect Van den Bergh reaction. The liver necrosis permits passage of bile into the blood stream and direct reaction is produced. When these factors are considered the biphasic reaction has real significance.

There are other conditions, particularly obstruction, which demonstrate all these reactions. During the first few days or hours after a sudden plugging of the common bile duct by a stone, the serum gives an indirect reaction. At this period the bile canaliculi are intact and the increased hepatic pressure causes a reflex which stops or reduces the excretory ability of the liver. This is similar to an anuria due to ureteral stone. As the pressure of the dammed-back bile becomes greater, small amounts of bile leak between the hepatic cells and into the circulation. At this time, a biphasic reaction is found. Later on, if the obstruction remains complete, so much bile is thrown back upon the circulation that the reaction becomes direct. This is due to much greater concentration of the unattached bilirubin. As the duct dilates round the stone and bile reaches the intestine, the Van den Bergh again becomes biphasic. Gradually the bile canaliculi regain their continuity and only the indirect reaction persists. This

continues only until the excretory function of the liver returns to normal.

Bilirubin is found in the urine in relation to this type of jaundice. When there is no discontinuity of the bile canaliculi, the pigment is not found in the urine. When there is sufficient liver cell destruction or intrahepatic pressure to separate the cells lining the bile canaliculi, bilirubin is generally found in the urine. In terms of Van den Bergh reaction, there is rarely, if ever, a bilirubinuria in association with an indirect reaction. There is, however, a bilirubinuria to be found in association with a direct reaction. The significance of this is that the kidneys are unable to separate bilirubin from its protein conjugation, but when it is lying free in the serum it is easily excreted by them.

Galactose tolerance. In order to assist in the differentiation of the jaundice of hepatitis and that of obstruction, a number of tests have been brought forward. The one now in vogue is the galactose tolerance test. The normal liver has the power to utilize galactose and store it as glucose, therefore, it was believed that the liver in which there was only biliary obstruction would be much more likely to retain its galactose-consuming function, than the one in which there was parenchymatous disease. In the early stage of obstruction, this supposition was found to be quite true but, as the obstruction continued there was a greater and greater necrosis of the liver cells; consequently the galactose test has in these cases, no basis to differentiate it from the cases of hepatitis.

Latent Jaundice. Latent jaundice is a term applied to conditions where the bilirubin content of the serum does not reach 4 units, so that the usual symptoms are missing. The hæmolytic type of this is seen in pernicious anæmia, anæmias due to worms and in the new-born. Its occurrence is of prognostic value when salvarsan is being given, as it is an evidence of the approach of poisoning by the drug. An obstructive type of latent jaundice occurs in cirrhosis. In this connection it is interesting to note that in the ordinary jaundice so common in the new-born (icterus neonatorum), the blood serum gives an indirect Van den Bergh's reaction, so that it is hæmolytic in origin. Before birth the foetus has a polycythæmia reaching about $6\frac{1}{2}$ millions per c.mm. On the second day after birth this excess has disappeared, and probably there will not be more than $4\frac{1}{2}$ millions. In a sense this polycythæmia may be regarded as a protection against the risk of loss of blood at birth. Once this has passed, hæmolysis occurs, and obvious hæmolytic jaundice may follow. The fact that latent jaundice is constant after birth supports this view. Severe jaundice in the new-born is generally due to suppurative pyelephlebitis from septic infection through the umbilical cord or to congenital syphilis. Rarely it results from congenital atresia of the bile ducts.

Dissociated jaundice has been described by French observers as the bile pigments going one way, the bile salts another. But as they did not take the condition of the blood into account judgment must be reserved on this. There may, indeed, be renal dissociation in obstructive jaundice, both pigments and salts being found in the blood, while only bile salts are filtered out by the kidney.

Urine. The best test for bile pigments is Gmelin's. The play of colours obtained by successive stages of oxidation with fuming nitric acid, green being the most important thing to look for. Rosenbach's modification of dipping filter paper into the urine and then placing a drop of nitric acid on the paper is the easiest way of performing the test. The green colour given on pouring tincture of iodine on to the surface of the urine is not so sensitive a test, and usually only succeeds when the jaundice is obvious. Huppert's test enables us to extract bile pigment from a urine containing other pigments. Ammonia and calcium chloride are added to urine, and the precipitate is then boiled with alcohol, acidified with sulphuric acid, when an emerald green solution results.

The only test of any value for bile salts in urine is Mathew Hay's test. Flowers of sulphur poured on to the urine sink if bile salts are present, owing to reduction of surface tension. No other test is sensitive enough to demonstrate the small quantity found in the urine, but a control with normal urine makes the test more reliable.

Blood. It has now been conclusively demonstrated that in jaundice the bile enters the blood-stream rather than the lymphatics, appearing there within two hours after experimental ligature of the bile-duct. Bile salts *in vitro* have a marked hæmolytic action due to their solvent action on the lecithin and cholesterin of the red corpuscles, and the serum of a jaundiced patient will hæmolyse foreign corpuscles readily, so that it may be impossible to carry out Wassermann's test, because hæmolysis occurs in all the tubes. But in the body the patient's own red corpuscles acquire a heightened resistance against bile salts which increases with the intensity of the jaundice. This sharply differentiates ordinary jaundice from acholuric family jaundice in which the red corpuscles are unduly fragile. Occasionally small subcutaneous hæmorrhages may occur, but more usually the hæmorrhagic marks on the skin are produced by scratching excited by the pruritus, or are really small telangiectases.

Heart and vessels. One of the most definite results of jaundice is bradycardia. High tension usually accompanies a slow pulse, but in the bradycardia of jaundice the pressure is low and the pulse dicrotic. High tension stimulates the cardioinhibitory centre in the medulla, and thus slows the heart through the vagus, but bile salts have a slightly depressing effect on the heart. Hence the slow pulse with low blood-pressure. The action can be demonstrated easily on the isolated heart of a frog. As the effect can be abolished by atropine,

bile salts probably act through the intracardiac endings of the vagus. The blood-pressure is also kept low by the toxic action of bile salts on the smaller blood vessels producing some degree of vaso-motor paralysis.

Central nervous system. Any severe toxæmic jaundice will be accompanied by marked nervous symptoms such as headache, delirium, and hepatic inadequacy caused by the action of the toxins on the liver and not to the jaundice. Indeed, bile salts are probably not produced in this condition, the liver being too damaged to elaborate them. A mild degree of poisoning of the nervous system by bile salts is, however, common in ordinary jaundice, causing headache and depression. Bile pigments and bile salts are generally found in the cerebro-spinal fluid removed by lumbar puncture.

Skin. Bile pigment usually appears in the skin soon after it does in the conjunctiva, but in the hæmolytic jaundice of pernicious anemia the latter usually escapes. In obstructive jaundice the colour of the skin gives no indication whatsoever of the amount of bilirubin present in the serum. In the deep green jaundice of prolonged obstruction there may be less pigment in the serum than in early stages when the skin is just beginning to show a yellow tinge. This suggests that the skin is used as an alternative organ of excretion, though, as will be pointed out later, it does not usually escape by sweat. It is merely stored up in the skin as if to free the more vital structures. Pruritus is a more troublesome symptom, but it is inconstant. Here the bile salts are responsible, as they cause alteration in surface tension which set up currents of lymph between the prickle cells. The patient indulges in much scratching, but without relief, for, as he often says and truly, the itching is beneath the skin.

Secretions. Saliva, tears, and milk are not bile-stained in jaundice. It is frequently stated that the sweat is bile-stained, but this is exceptional. Nasal and bronchial mucus is not tinged with bile. Inflammatory and passive exudates are, however, invariably bile-stained. Thus if mastitis occurs in jaundice the milk will be coloured with bile. The expectoration in bronchitis is not coloured, but if pneumonia occurs as a complication bile at once appears in the sputum. In a case of jaundice without pneumonia the occurrence of bile-stained sputum is of serious import, being evidence of heart failure. Fluid in the pleural or of abdominal cavity, being either the result of inflammation or of passive exudation, will accordingly be coloured by bile in jaundiced patients.

• In conclusion, it will be observed that apart from an unpleasant but harmless discoloration produced by bile pigments all the important symptoms in jaundice are due to bile salts. Their absence from the intestine causes steatorrhœa and wasting from deficient absorption of fats, increased intestinal putrefaction and constipation. Their presence

in the blood causes bradycardia, headache, depression, pruritus and sometimes subcutaneous hæmorrhages.

TREATMENT. The treatment of jaundice must depend upon the cause, but the following general principles are applicable. During the initial stages the patient should be confined to bed. Although calomel is only indirectly a cholagogue it may be given in doses of $\frac{1}{2}$ gr. every hour for six doses, this often relieves the vomiting, and has the additional advantage of being aperient without causing drastic purgation, which should be avoided. Ten hours after beginning the calomel treatment, a seidlitz powder should be given, for repeated doses of calomel, if not effective in opening the bowels, may set up mercurial stomatitis. Alkalies are indicated as solvents of mucus in catarrhal cases, and, if the vomiting persists, may be combined with 10 gr. of bismuth salicylate. As soon as the state of the stomach permits, the more active sodium salicylate should be substituted as a diluent and disinfectant of the bile. Hexamine is frequently used in an alkaline medium along with salicylates as a biliary antiseptic. Preparations of bile salts, *e.g.*, decholin and felamine have proved efficacious in certain cases. In toxæmic cases the patient should be encouraged to drink large quantities of barley water and the like. With the onset of severe symptoms it is advisable to purge freely and to give an intravenous infusion of a pint of normal saline at body temperature. Venesection has the advantage of removing toxins while infusion dilutes them. Theocinacetate in 2 gr. doses is a useful diuretic. As dextrose is the most easily metabolized food-stuff in this state, it should be given by mouth or rectum.

In even mild cases the diet will naturally be light. Milk is usually regarded as the mainstay, but owing to its comparative richness in fat it is not really suitable, and is often much disliked by the patient. It is preferable to give barley water flavoured with lemon, with the white of an egg, and a teaspoonful of plasmon to each half pint. Tea is usually forbidden, though it is difficult to see on what grounds, jaundiced patients often crave for it, and if made in the Russian fashion without milk, but with a slice of lemon in it, it seems free from objection. If the practitioner feels reluctant to abandon milk, it should be separated or thoroughly skimmed to get rid of as much fat as possible. A grain of sodium citrate should be added to each ounce of milk, to diminish curdling. Benger's food made with water, cow's foot jelly and lemon sponge can usually be taken without difficulty. Alkaline mineral waters may be given freely.

When the bile pigments have returned in the fæces in obstructive cases, the patient feels much better though still jaundiced; he can now get up, and the diet should be cautiously increased. There is sometimes considerable depression during convalescence, for which strychnine and calumba may be given. Dilute, nitro-hydrochloric acid in 10 min. doses is often recommended, but should not be given until

all signs of obstruction have passed off. For pruritus, hot alkaline baths may be tried, or some of the following preparations : a lotion of 1 dr. creolin and 1 oz. glycerine made up with 10 oz. of water ; an ointment of 20 gr. camphor, 30 gr. menthol and 1 oz. vaselin ; a dusting powder of $1\frac{1}{2}$ dr. camphor, $\frac{1}{2}$ dr. zinc oxide and 1 oz. starch powder ; a paint or inunction of $2\frac{1}{2}$ dr. ichthyol, 3 dr. absolute alcohol and 2 oz. ether. Other preparations which may help are Richioffs superfatted ichthyol salicylic acid soap, prepared by inucin of Cologne, or 10 per cent. of anæsthesine in olive oil. Thyroid extract in $\frac{1}{2}$ gr. doses may help by diminishing the formation of bile salts.

KALA-AZAR. See page 436.

LABORATORY EXAMINATIONS IN GENERAL PRACTICE.

Routine examinations. 1. A general qualitative and microscopical examination should be done for all specimens of urine. A quantitative examination of some of its important constituents such as sugar, chlorides, phosphates, sulphates and urea should be undertaken. The estimation of hæmoglobin percentage, a red cell count and a total and differential count of white cells of the blood should be made. The coagulation time and blood grouping are essential in some surgical cases only. In all chronic complaints, a Wassermann test should also be done. The sputum should be examined for tubercle bacilli and cultured if necessary. The stool should be examined for the ova of parasitic helminths and a test for occult blood should be undertaken. The cultures of swabs taken from the nasal and pharyngeal regions are required in case of children suffering from chronic cold.

2. To investigate into the causes of prolonged fever, urine should be examined for pus, centrifugalised and examined for tubercle bacilli. A cultural examination may also be made for *Bact. coli*. In females, smears from the urethra and cervix should be cultured and examined for Gram-negative diplococci. A total and differential leucocyte count is also indicated in such cases. Cultural and agglutination tests of blood should also be undertaken. Blood films should be examined particularly for malarial parasites and microfilaria. The sputum should be repeatedly examined for tubercle bacilli and it should be cultured and an animal inoculation test performed to confirm a diagnosis. A tuberculin test is most essential. If cerebral symptoms are present a lumbar puncture should be performed and the cerebro-spinal fluid stained and examined for cells and bacteria. If ascites is present, the ascitic fluid after paracentesis should be examined for cells and bacteria. A cultural examination of the fluid for bacteria should also be done and an animal inoculation test performed for tubercle bacilli.

3. In cases of exophthalmic goitre the basal metabolic rate should always be estimated. In Hodgkin's disease, tuberculous adenitis and malignant diseases biopsy of the part is essential. In cirrhosis of liver, icterus index and bromsulphthalein tests should be done. In cases

of gastro-duodenal ulcers the gastric contents should be examined for total acidity and a fractional test meal examination should be undertaken and the stool should be tested for occult blood. Stomach washings in children may sometimes show tubercle bacilli.

4. In cases of emaciation the following causes such as neurosis, febrile diseases, tuberculosis, Grave's disease, diabetes, malignant disease, inanition should be borne in mind. The urine should be examined for sugar, albumin, casts, etc.; the sputum, specially the morning specimen for tubercle bacilli, stool for gross appearance, occult blood, mucus and parasites. A culture may be done if necessary. The gastric contents should be examined for appearance, retention, odour, acidity and blood. Blood should always be examined for Wassermann reaction in these cases. The basal metabolic rate should also be estimated to detect hyperthyroidism.

5. In all cases of anemia, the estimation of the percentage of hemoglobin, a total and differential white cell count and an icterus index examination should be undertaken. A red cell count, a cell volume estimation, testing for red cell fragility and a platelet count are also essential in these cases.

6. The percentage of sugar in blood in cases of diabetes, obesity, arteriosclerosis, gall bladder disease, and suspected hypoglycæmia should be estimated. The fasting blood sugar should also be estimated. The carbon dioxide combining power of plasma in ketosis condition in diabetes, uræmia with nitrogen retention, protracted vomiting, and intestinal toxæmia should be known. The carbon dioxide combining power of the plasma can be determined by the Vanslyke's manometric apparatus or by Fradkin's where available. A strong acid is added to the plasma and some vacuum is created to collect the carbon dioxide gas liberated. This is recorded in cubic centimeters per 100 c.cm. of blood plasma (volume per cent.). Estimation of the blood urea should be undertaken in these cases. There is no necessity for estimating creatinine in blood unless the urea nitrogen is over 30. The uric acid in the blood in cases of gout and also calcium in the blood in osteomalacia, tetany, rickets and other metabolic disorder diseases and the cholesterol in blood in nephrosis and gall bladder diseases should be estimated.

7. In cases of acute diarrhœa, the stool should be cultured for bacilli of dysentery, typhoid, cholera, and entamœba histolytica. The gastric contents should be examined for total acidity. A blood culture should be undertaken for enteric fever with a total and differential white cell count. A high icterus index is indicative of acute arsenic poisoning. In all cases of chronic diarrhœas a proctoscopic examination is of utmost importance to exclude local causes. The stool should also be examined for occult blood, parasites or their ova. A positive urobilinogen test in urine indicates cirrhosis of the liver or arsenical poisoning.

8. Jaundice and liver functions. In these cases the urine should be examined for bile, urobilinogen, diastase and sugar. Bile is present in obstructive and catarrhal jaundice and is absent in hæmolytic jaundice. Urobilinogen is present in early disorders of the liver but is absent in complete obstruction of the common bile duct. Diastase and sugar should be looked for in malignant diseases or necrosis of the pancreas. A positive icterus index of blood signifies a severe jaundice. A Wasserman reaction of blood should be done to detect syphilitic affection of the liver. In case of familial hæmolytic jaundice the fragility test of red blood cells should be performed. A radiogram of the gall bladder after administration of some opaque dye is helpful in diagnosing gall bladder disease.

LABORATORY TESTS IN VENEREAL DISEASES. In acute cases treatment should be withheld for twelve hours and then the urethral discharge should be microscopically examined for cells and bacteria. In chronic cases no treatment should be given for 24 hours and then the following tests for urine should be undertaken :—

(a) *Two bottle tests.*

Types of urethritis.	First specimen	Second specimen
(1) Anterior urethritis (early).	Cloudy with shreds.	Clear.
(2) Anterior urethritis (late).	Turbid with shreds.	Clear with shreds.
(3) Posterior urethritis with prostatitis.	Turbid with shreds.	Clear with shreds.

(b) *The urethral discharge and prostatic secretions after prostatic massage should be microscopically examined.*

In case of a genital sore it should be washed with normal saline and then scrapings should be taken from it and examined for spirochaetes by the dark ground illumination method on three successive days. The blood should be examined for Wasserman reaction every month for three months following a genital sore.

In females, smears from cervical discharge should be taken and examined microscopically for the exclusion of infection with *trichomonas vaginalis*.

LATHYRISM. See page 1036.

LEISHMANIASIS. VISCERAL LEISHMANIASIS OR KALA-AZAR. *Diagnosis.* The diagnosis of kala-azar by clinical signs and symptoms is not to be relied on. The demonstration of leishmania is usually necessary.

Demonstration of leishmania. The following methods may be adopted :—(a) *Spleen puncture.* The patient is prepared by withholding food for at least 3 hours before the operation and a dose of calcium lactate 20 to 30 gr. is given about half an hour before the puncture; this dose is repeated immediately after the puncture. A dry sterilised 5 c.cm. syringe with a medium-sized needle is recommended. The

operation is performed in two steps, the skin over the site of puncture having been sterilised, is punctured. The puncture should be made about an inch below the costal margin and midway between the anterior and posterior borders of the spleen. Secondly, with the syringe at an angle of 45° with the patient's body, the needle is plunged through the abdominal parietes into the spleen in an upward and outward direction. The plunger is withdrawn once or twice rapidly and the needle withdrawn. It is advantageous to have an assistant to steady the spleen during the puncture, if the special spleen-puncture syringe is not used. (b) *Liver puncture.* The patient is prepared as for a spleen puncture. The liver is usually punctured through the 8th intercostal space in the mid-or posterior axillary line. The material from the syringe is smeared on a slide and examined after being stained with either Giemsa's or Leishman's stain. (c) *Examination of peripheral blood.* Success in this examination is largely dependent on the preparation of the slide. The best slide is one that has a blood film with straight edge to it, where the greater number of white blood cells will be found. To prepare such a slide the smear is begun in the usual way, but when it is seen that the blood between the two slides is getting exhausted the slide used as the smearer is flicked abruptly upwards. With a little practice this movement will produce a straight end to the smear. The slide is stained and the white blood cells examined for the contained Leishman-Donovan bodies. (d) *Blood culture.* One or two cubic centimetres of blood are withdrawn under strictly aseptic conditions and about a cubic centimetre is dropped into a tube containing 10 c.cm. of sterile citrated saline. The cells are allowed to settle. After sedimentation two or three tubes of N.N.N. medium are inoculated with the corpuscles with a sterile pipette, and incubated at 22° to 24°C . The first tube should be examined on the 10th day, but the cultures cannot be declared negative until at least a month has elapsed. The material from the spleen or liver puncture can be similarly cultivated.

Serum reactions. (a) *Napier's aldehyde reaction* (see page 446). (b) *Chopra's antimony test* (see page 446). (c) *Chopra's finger-prick blood test* (see page 447).

TREATMENT (see page 436). Neostibosan and urea-stibamine are two of the best drugs. Freshly prepared neostibosan is given in doses of 0.2 to 0.3 gm. for an adult of 100 lb. weight in a five per cent. solution. Injections may be given every day commencing with a dose of 0.2 gm. increased to 0.3 gm. until a total dosage of 2.3 to 2.9 gm. is reached. In resistant cases a course of 12 injections commencing with 0.3 gm. reaching a maximum of 0.5 gm. should be given and repeated after 14 days' interval. Urea stibamine is used in smaller doses commencing with 0.05 gm., 0.2 to 0.25 gm. being the maximum used at an injection. It is usually given every other day.

Test of cure (see page 446).

DIAGNOSIS OF DERMAL LEISHMANIASIS. Leishman-Donovan bodies are easily demonstrated from a nodule in this condition. The nodule should be snipped off and a smear made from the cut surface; this should be stained by Leishman's method and parasites will usually be seen in fair numbers. In the depigmented patches they can be demonstrated by cultural methods; a small quantity of sterile citrated saline is injected under the dermis and as much of it as possible is sucked back into the syringe. This is then inoculated into one or two tubes of N.N.N. medium and incubated at the usual temperature. A provocative injection of antimony may be given with advantage. Sandfly feeding is also helpful.

Treatment. More intensive treatment with pentavalent and trivalent compounds of antimony is necessary in this condition. Iodides are also given by mouth.

ORIENTAL SORE. *Laboratory diagnosis.* (1) Examination of the stained smear of the material obtained by scraping the edge of the ulcer. (2) Culture of the causal organism on N.N.N. medium. In obtaining material for this purpose it is necessary to sterilise the unbroken skin at the edge of the sore.

Treatment. Unless the lesions are numerous, a condition which is uncommon, the sore should be treated by local infiltration with 1 to 2 per cent. solution of acid berberine sulphate.

Antimonial injections are advocated only when the lesions are too numerous to be dealt with by the local infiltration method.

ESPUNDIA. It is a form of American Leishmaniasis resembling oriental sore. It produces ulcerating granulomatous lesions of the mucous membrane of nose and mouth.

Treatment. (1) Antimony injection as in kala-azar. (2) Locally, (a) aseptic dressings, (b) carbon dioxide snow, (c) X-ray treatment, (d) berberine sulphate injection $\frac{1}{2}$ gr. in 1 c.cm. once a week by local infiltration, (e) zinc oxide ionisation.

LUMBAGO. This denotes a pain in the lumbar muscles due to inflammation of the connective tissue between the muscle fibres. It might also extend and affect the fasciae, ligaments, tendons and nerve sheaths in the lumbar region of the body. It is met with in persons of both the sexes and in all stations of life. In most cases, the cause can be attributed to exposure, wet or cold or to a chill, but the exciting cause is frequently a strain or even a trauma to the lumbar muscles. This combination of trauma and exposure in the causation of fibrositis is mostly seen in the male sex and during the active periods of middle life. Besides, some form of chronic or subacute infection is said to be responsible for the condition. Gout, endocrine dysfunctions and the influences of changes in climatic conditions are also suggested aetiological factors. Lumbago from physical injury of the tissues as a result of a blow or sudden wrench is a form of fibrositis where the

devitalised tissues are invaded by bacterial toxins, the sites of infection being in foci like teeth, tonsils, nasal sinus, intestines and the biliary apparatus. This type of fibrositis may start with minor pains in the back but frequently its onset is acute. The spasm of the muscles relaxes at times and the patient is then much relieved. The pain is referred to the lumbar muscles and aggravated by movements of the lumbar spine. The cramp-like pain is at first limited to the muscles which may afterwards diffuse and spread over the ilium or into the loin. The lumbar regions on examination are found to be very tender at this stage and the patients are usually most comfortable lying on the back on a firm bed. Occasionally the inflammatory process may extend to involve the sheath of the sciatic nerve, resulting in sciatica. Generally an acute attack takes 3 to 4 weeks to subside, but is liable to recurrences. In chronic cases of fibrositis organisation of fibrous tissue and thickening of the walls of the blood vessels and nerve sheaths in the area involved takes place.

TREATMENT. The general treatment of this type of fibrositis includes absolute rest in bed during the acute stage of the disease, avoidance of over fatigue and occupations involving strains to the part, thorough investigation for septic foci in the body and their eradication when detected, regulation of the bowels and elimination of dietetic principles leading to dyspepsia, colitis, obesity and lastly avoidance of sudden changes in temperature. Drugs that are mostly used are analgesics including the coal tar series, aspirin, phenacetin, etc., and in acute lumbago the relief of pain may be obtained with codeine or barbiturates, allonal or veramon. Sometimes the intramuscular injection of $\frac{1}{2}$ gr. of morphine or 5 c.cm. of a 1 per cent. solution of hydrochloride of quinine and urea may be required to inject deeply into the tender nodule for the relief of acute pain. If there is a tendency to gout, atophan 10 gr. three times a day for three days in the week is of benefit. The drug, however, should not be used where the hepatic functions are deranged. For non-specific protein therapy see page 1418. Endocrine therapy is of particular value in cases where glandular deficiencies are suspected. Physical therapy is more effective than drugs in these cases. During the acute stage absolute rest in bed should always be aimed at and relief of pain may be obtained by immobilisation with strapping, by analgesic liniments and poultices and especially by local radiant heat. Ionisation with potassium iodide and salicylates, diathermy and local ultra-violet light, are also of benefit at this stage. Elimination of toxins may be encouraged with spa treatment and measures should be adopted to promote the healthy action of the skin, such as by radiant heat, vapour baths, etc. Absorption of exudates is generally aided by heat, elastic pressure, counter-irritation and ionisation and breaking down of the fibrous tissues by dry or douche massage. When the pain diminishes in severity, deep massage of the lumbar muscles should be employed

combined with gentle active and passive movements of the back. In chronic long-standing cases the body resistance should be raised by means of general ultra-violet light and wasting of muscles prevented by massage and faradic stimulation.

MALARIA. DIAGNOSIS. (1) *Thin film.* Stain by one of the following modifications of the original Romanowsky stain. (a) Leishman's stain which is both a fixative and a stain. (b) Giemsa's stain. In using this stain previous fixation with methyl or absolute alcohol is necessary. (c) Combined Leishman and Giemsa's stains. (2) *Thick film.* Dehæmoglobinise with a mixture of a solution of glacial acetic acid and tartaric acid. Fix with methyl alcohol. Wash very thoroughly with slightly alkaline distilled water. Stain by combined Leishman's and Giemsa's stains or by Giemsa's stain only. (3) *Cultivation of parasites.* Take 5 c.cm. of blood and defibrinate in a flask containing glass beads. Into the bottom of a small test tube ($12\frac{1}{2} \times 1\frac{1}{2}$ cm.) introduce one drop of 50 per cent. dextrose solution with a capillary pipette; aspirate off the defibrinated blood from the flask and introduce it into the tube. Warm the upper part of the tube and put a rubber cap on. Incubate the culture tube in a vertical position at 37°C . Cultures should be examined at different intervals up to 48 hours or more. (4) *Enumeration of parasites.* A suspension of fowl's cells is prepared and standardised according to Sinton's technique. Equal volumes of the blood and the fowl cell suspension are taken with a capillary pipette and blown out on a clean slide. The two fluids are thoroughly mixed by drawing the mixture in and out of the pipette a number of times and then a thin film is drawn on a clean slide. In making a count the ratio of the number of fowl corpuscles to the number of parasites is determined and from the known strength of the standard suspension of fowl corpuscles one can calculate the number of parasites per c. mm.

TREATMENT. (1) *Cinchona alkaloids* (see page 516). Quinine sulphate 10 gr. twice daily; totaquina or cinchona febrifuge 10 gr. twice daily. Whether given in mixture or tablet form, a dose of an alkaline mixture is always given half an hour before. The course of treatment is 7 to 10 days and for every fresh attack or relapse this course should be repeated. Cinchona alkaloids have no effect on the sexual forms of malignant tertian parasites. (2) *Plasmoquin.* It is the only drug that destroys crescents; 0.01 gm. twice daily for two or three days is sufficient to cause disappearance of the crescents from the peripheral blood. In safe doses it has little effect on *P. vivax*, *P. malariae* and on the asexual forms of *P. falciparum*. It should not be used for routine treatment of malaria. (3) *Atabrin.* 0.1 gm. thrice daily for 5 to 7 days eradicates all forms of *P. vivax* and *P. malariae*; also the asexual forms of *P. falciparum*. Like cinchona alkaloids it has no effect on the crescents.

MALIGNANT DISEASE. It commences as a local affection in one spot or an area and possibly in one individual cell. As the disease

spreads, a local tumour or a new formation of tissue develops, which sooner or later makes itself manifest as a visible or a palpable swelling. Symptoms of pain or disturbance in the normal function of the parts of the organism supervene. Malignant disease, in its early stages is often painless and if a cure is to be obtained by treatment, the earlier the patient is submitted to proper measures the greater are the chances of success. The onset of an abnormal secretion or excretion from the part affected, especially when marked by the presence of blood or blood-stained material, should always be seriously considered and the patient submitted to appropriate examination and investigation. This is especially the case when blood or sanguinous materials appear in the stool, urine, vaginal discharge, discharge from the nipple in women, or in discharges from or in connection with one or other orifices of the body. While taking the history from the patient, the chronological onset of the various symptoms and signs which bring the patient for observation and examination should be carefully ascertained as it is of considerable importance for the clinician to know the duration of the growth.

METHODS OF EXAMINATION. Clinically the examination comprises visual observation and palpation by which the position, extent and relations of the tumour are ascertained and also its connection with adjacent tissues or organs. Its consistency, whether solid or fluid, should be determined. The extent of the swelling and its relation with the surrounding tissues should be defined and the presence or absence of pain on manipulation noted. The tumour should be transilluminated to determine the presence or absence of opacity. Most malignant tumours are opaque. The presence of a solid swelling of recent development with indefinite margins, almost painless on manipulation and opaque on transillumination generally suggests early malignancy. After the local examination of a tumour is completed, the lymphatic glands draining the affected area should always be palpated. Solid enlargement of lymphatic glands helps to confirm a diagnosis of malignant disease. When a swelling has been detected or suspected near or adjacent to one of the normal orifices of the body, examination should be made with the finger or failing this, visually, through one of the special instruments available for the purpose. These instruments should however only be used by experts. The use of the œsophagoscope, bronchoscope and sigmoidoscope by untrained observers has often led to the injury of the part examined and moreover too much reliance cannot be placed upon their interpretations.

Microscopical examination. Materials such as blood-stained matter or solid particles obtained from a supposed malignant tumour or ulcer, should be submitted to microscopical examination. Very often, characteristic tissues suggesting malignant growths may be revealed.

Biopsy. In a readily accessible swelling such as a tumour involving the tongue, the floor of the mouth, the lower portion of the rectum

or the region of the cervix uteri, the clinician should remove a portion of it and submit it to a histological examination. Such a procedure is likely to spread the tumour by the lymph or the blood channels if it is malignant. This can be probably avoided by the use of a diathermic knife. Whenever possible, the portion selected for removal should be at the junction of the normal tissue and the suspected tumour and it should be cut at right angles to the surface.

Biochemical examination. It includes an ability to diagnose cancer from an examination of the blood or the blood serum. One of the latest of these is that claimed by Bendien by a flocculation test of the blood serum.

X-ray. Under certain circumstances, radiograms of the parts give most important aid in the early diagnosis of malignant disease especially in suspected disease of the stomach and alimentary tract or the lungs with no associated tumour or swelling. Radiograms are of particular value in the investigation of suspected tumours of bone.

Exploratory operation. An exploratory operation is often desirable to confirm a diagnosis and ensure subsequent successful treatment. The clinician, the radiologist, the clinical pathologist and possibly the anatomist, should all co-operate to make the diagnosis a correct one, at the early stage of the disease. As soon as the diagnosis is confirmed by an exploratory operation, it is often desirable to completely remove the diseased tissues where possible and if not to perform some other operation for a temporary relief of the patient's condition.

For the treatment of malignant growths by deep X-ray therapy and radium see page 135 and 141.

MALTA FEVER (Undulant fever). See page 907.

MEASLES. The disease seems to be due to a filterable virus which is present in the patient's blood and can be transmitted to other susceptible human beings and monkeys. One attack confers immunity against subsequent attacks. The highest attack rate occurs in children between the ages of 3 and 4. Fatality is at its maximum in the first year of life and it remains high till the third year. *Ætiological factors* are exposure to infection, under-nourishment (victims of avitaminosis), debility and unfavourable hygienic conditions of living. Incubation period is 14 days.

DIAGNOSIS. It is made from symptoms of coryza, fever, and characteristic rash.

TREATMENT. No specific remedy is known. (1) *Sick-room.* The patient should be entirely isolated, the room should be large, well ventilated and sunlight should have free access. (2) *Diet.* Fluids tolerated are sweetened lemonade, barley water, lime whey, milk and plain water. (3) *Attention to the mouth and nasal passages* is most essential to prevent subsequent complications such as otitis media, suppurative adenitis and broncho-pneumonia. Laryngitis disappears with

the appearance of the exanthem. Mild antiseptic alkaline lotions like sodium bicarbonate and glycothymoline are useful for cleansing the mouth. A prescription with potassium chlorate taken internally is almost specific in alleviating stomatitis and preventing ulceration and cancrum oris. (4) If diarrhoea is present grey powder and lime water are useful. (5) Treat on general lines if complications such as pneumonia and emphysema set in. (6) Latest so called specifics are pyramidon, ultra-violet ray therapy, but results are not encouraging. (7) *Serum therapy.* Convalescent serum has been used both in prophylaxis and treatment in the acute stage. Donors must be healthy and not exposed recently to any infectious disease. The blood is withdrawn 10 to 14 days after deferescence and amounts up to 20 c. cm. from a child of 5 years, 100 c. cm. from a child of 10 years and 250-500 c. cm. from an adult may be taken. The clear serum is withdrawn and tested for W. R. and sterility. It is customary to filter the serum and add phenol or other preservative; the ampoules are stored at 4°C. To afford complete protection a minimum dose of 5 c. cm. of the serum is given intramuscularly within the first five days after exposure to infection. To produce an attenuated attack the same dose is injected between the 6th and 9th day after exposure or preferably half the above dose is given before the 6th day. Sometimes whole blood injection from parents to children contacts is given. The approximate dose in such cases is double that of convalescent whole blood and 4 times that of convalescent serum. After such sero-attenuation, the attack is always mild and uncomplicated. (8) Mixed vaccines may be used when resolution is delayed or recovery incomplete. (9) Moline method of disinfection. The contacts are dosed with eucalyptus oil and the patient's tonsils and pharynx are swabbed with 10 per cent carbolic oil and he is put in a gauze tent sprayed with eucalyptus. (10) Aspirin 5 gr., Dover's powder 2½ gr. and phenacetin 2½ gr. are useful. Alkaline mixtures should be prescribed during the febrile period and sedative expectorants are given for coryza.

MIGRAINE. This is usually described as a paroxysmal affection with severe unilateral headache, preceded by visual phenomena and followed by nausea and vomiting. Sometimes one symptom is sufficient to represent an attack of migraine. The characteristic periodic headache with other symptoms such as irritability, confusion, loss of appetite, giddiness, photophobia, etc., is diagnostic of migraine. Though termed hemicrania, the headache is not always unilateral. Repeated attacks of migraine result in severe mental and physical prostration and this is again followed for some time by severe neuralgic pain over a limited area of the head or face. Inequality of pupils, persistent hemianopia, ocular paresis and persistent hemiplegia with or without aphasia or agraphia have been seen as sequelae to chronic migraine. Several clinical types of the disease are recognised and theories have been advanced to explain its nature; the treatment is resolved according

to ætiological factors: (1) *Alimentary type*. Dysfunction of the gastro-intestinal tract, including the biliary apparatus, has been thought to be a potent ætiological factor and bilious, abdominal and duodenal types of migraine are recognised. These facts cannot be ignored as the treatment of hepatic dysfunctions with glucose, decholin tablets, etc., has relieved many migraine attacks. (2) *Allergic and dietetic type*. Migraine has been regarded as an anaphylactic shock. Non-specific protein therapy has also been tried on the basis of such an assumption though sometimes the taking in of a particular article of diet has precipitated an attack and the treatment has been to exclude this article from the dietary without effect. (3) *Endocrine type*. Endocrine dysfunction has been regarded as a common ætiological factor. This is particularly marked in ovarian dysfunction where migraine occurs at the menstrual periods. Excellent results have followed the administration of *emmenin complex* (Collip's placental hormone) $\frac{1}{2}$ to 1 dr. twice daily, except during the menstrual period, in such cases. Thomson recommends three injections of theelin, each 1 c.cm., to be given in the week before the period is due. It is suggested that such treatment causes a diminution in size of the pituitary which would otherwise cause headache by pressure against the sella turcica or a large diaphragma sellæ. (4) *Metabolic type*. Errors in diet, faulty metabolism and defective elimination of waste products are considered to be causal factors in precipitating an attack of migraine. The onset of migraine in the early hours of the morning, starvation, prolonged physical strain and its subsequent relief by administering glucose, all go to confirm the metabolic factor. (5) *Ocular type*. Subjects with defective vision due to errors of refraction and slight ocular muscle imbalance are known to suffer from intense unilateral headache. Correction of such defects with correct glasses has very often relieved the distressing symptom. (6) *Para-epileptic and cerebral type*. The close similarity between migraine and epilepsy has led to the treatment of the para-epileptic type by bromides, luminal and ketogenic diet. Symptoms of cerebral tumours and other intracranial lesions closely simulate those of migraine and this led to the recognition of the cerebral type of migraine. (7) *Psychological type*. Psychological factors, such as mental overwork, anxiety, 'suppressed rage and humiliation', play an important role in the ætiology of migraine. Psychotherapy has improved many such cases. (8) *Vasomotor and sympathetic type*. Migraine is thought to be the result of a localised intracranial oedema. The advocates of the sympathetic origin of migraine hold that the disease is due to an excessive stimulation of the sympathetic system resulting in spastic contraction of the cerebral arterioles with their subsequent relaxation. Calcium therapy and the administration of irradiated ergosterol have been beneficial in these cases. Lennox tried ergotamine tartrate in the treatment of migraine. It is probable that the benefit derived from ergotamine in migraine is due to its effect upon the smooth muscle of the cerebral blood vessels. It is

likely that ergotamine abolishes the pain by increasing the tone of the cerebral vessels and hence diminishing their stretch. The doses of the drug recommended are 0.5 mg. subcutaneously or 1.0 mg. by the mouth. If the headache is not relieved the dose can be repeated after an interval of 2 to 3 hours. The drug should not be used in pregnancy and cardiovascular diseases. A few untoward symptoms such as vomiting, increase in systolic blood pressure, decrease in pulse pressure, and bradycardia may be met with after its administration.

TREATMENT. Bearing all the aetiological factors in mind a thorough investigation of the case, including radiographic and biochemical examinations where possible, is necessary before adopting treatment. Treat the patient during and in between the attacks. During the actual seizure, the patient should be removed to a dark quiet room and sedative drugs such as veramon (6 gr.), phenacetin (10 gr.), caffeine citrate (5 gr.), comprial (3 tablets) etc., may be tried to relieve the pain; luminal ($\frac{1}{2}$ to 1 gr.) has given good results. Between the attacks, drugs discussed under the aetiological factors may be tried. A useful prescription in migraine is : sodium bromide 10 gr., nitroglycerine 1 min., strychnine hydrochloride solution 5 min., dilute hydrochloric acid 10 min., tincture of gelsemium 5 min., and chloroform water up to $\frac{1}{2}$ oz. This is given three times a day.

MOLLUSCUM CONTAGIOSUM. This is an infectious type of epithelial overgrowth consisting of rounded or flat papules from pinhead to bean size, pearly gray, with a central depression from which a caseous plug, called the molluscum body, may be squeezed. The molluscum body contains only degenerated epithelial cells and keratin. The principal sites of involvement are the face, hands and genitals, but they may be widely distributed.

TREATMENT. Manual expression and cauterisation with trichloroacetic acid diluted or undiluted.

MUMPS. It is an acute infectious disease characterised by parotitis and constitutional disturbances. Mumps is due to a filtrable virus present in saliva (Kermorgant). The incubation period is longer than general infectious diseases and is usually between 18 to 22 days. One attack usually confers immunity for the rest of life. A second attack is very rare. *The complications.* Orchitis is common, but atrophy of the testis is rare; pancreatitis is rare; encephalitis or meningo-encephalitis, meningitis, polyneuritis, arthritis, occur.

DIAGNOSIS. (1) Make a careful examination of the fauces to exclude hypertoxic diphtheria. (2) Presence of orchitis in males in absence of gonorrhoea and with a history of facial swelling. (3) Lumbar puncture. In genuine mumps cerebrospinal lymphocytosis is constant and marked in early stages and lasts for several months.

TREATMENT. (1) Rest in bed during the acute stage. (2) Erotic excitement of any kind should be avoided as well as any sort of violent

exercise as riding or cycling, for some weeks after the attack. (3) Mouth to be kept clean by gargles and mouth washes, potassium chlorate 10 gr., tincture of lavender 10 min., glycerine acid boric 1 dr., water up to 1 oz., to be diluted with an equal quantity of warm water before use. (4) Locally, hot fomentation, ichthyol and belladonna paint are useful. (5) Injections of salvarsan and other arsenicals are advocated. (6) Orchitis ; suspensory bandages, lead and opium compresses.

MYIASIS. It is due to the invasion of the skin and subcutaneous tissue by the larvæ of *Cordylobia anthropaga* or an allied species of fly. This condition may be cutaneous, nasal or intestinal. It is not known how infection takes place, but it is possible that the fly lays its eggs, apparently about 150 at a time, on the ground, and that the larvæ creep from the earth on to their human hosts, perhaps when the latter are sleeping on the ground. It is also possible that the fly lays its eggs on clothing, as when the latter is put out to dry it exhales the odour of sweat and so attracts the fleas. There is no evidence to show that oviposition takes place directly on the skin. Its usual host appears to be the domestic dog, the skin of the scrotum being specially affected. The lesion produced is like a small boil or urticarial wheal, in the centre of which there is an opening which may be obscured by the discharge or it may be patent.

TREATMENT. Instillation or local application of pure chloroform is the usual remedy. Insufflation with calomel has also been tried with success.

NAUSEA. See page 1413.

NEURALGIA. It denotes pain which follows the distribution of certain nerves in the body. It is generally due to fibrositis confined to the connective tissue forming the sheath and surrounding the fibres of the nerve. Besides, an undue toxic state of the blood is a most common factor in the causation of pain. The toxins in the blood directly irritate the nerve and as in gout, by causing a vaso-constriction, deprive the nerve of its nutrition. It is also suggested that the pain is due to congestion or a local vaso-dilatation in the neighbourhood of the nerve. An irritant causing fatigue of the nerve is held to be another ætiological factor. The condition may affect any nerve in the body but the nerves commonly involved are the sciatic, brachial, peroneal, intercostal, occipital, facial and trigeminal. The involved nerve is found to be pink in colour and swollen and on puncture of its sheath, drops of fluid exude from between the fibres of the nerve. The pathological changes are usually confined to the interstitial tissue but sometimes a true neuritis or nerve atrophy results from pressure of scar tissue on the nerve elements. Sensory disturbances, such as paræsthesia, tenderness and pain aggravated by stretching

of the nerve often appear and in severe cases motor paralysis or trophic changes are also met with.

SCIATICA. Pain along the sciatic nerve may be due to causes other than fibrositis. Sciatica may be caused by a loaded rectum, by uterine and ovarian displacements, by tumours and disease of the spinal cord itself and such possible factors should always be carefully and exhaustively investigated before the pain is pronounced to be due to neuralgia, and treated as such. It is important to determine whether the pain is due to pressure, or to some factor in the nerve itself or in its sheath. If caused by pressure the pain will not be sensibly aggravated when the nerve is put on the stretch, it may be to some extent relieved by the process, whereas, when the mischief is in the nerve or its sheath, the stretching will obviously increase the pain. In order to set this point at rest, the patient is placed upon his back and the pelvis firmly fixed against the bed by an attendant. The limb on the affected side, which must be kept fully extended at the knee, is then gently and gradually raised by the examiner until it is at right angles to the couch. This will put the nerve on stretch and if no aggravation of pain results, then the cause is to be sought outside the sheath of the nerve. The condition starts with pain in the back of the leg aggravated on straightening the knee, especially if the thigh is flexed. Afterwards the pain becomes acute and constant and the course of the nerve becomes very tender on palpation. The distribution of pain and tenderness however depend on the part of the nerve affected. In addition to the characteristic pain in sciatica, the presence of wasting of the gluteus maximus muscle considerably aids the diagnosis. Points of maximum tenderness are located at definite sites of the distribution of the nerves. The duration of an attack is variable and the ultimate prognosis is generally hopeful.

Treatment. The treatment of sciatica in the early stage demands rest, counter-irritation and analgesic drugs for the relief of pain. In cases of strain, correction of the fault is of the first importance. The exact manipulation required depends, of course, on the lesion. If manipulation is very painful a preliminary course of treatment in form of heat, local massage, etc. to reduce congestion is indicated. Radiant heat is most useful, and the infra-red rays have been used with good effect, and ultra-violet light is of some value in the most superficial forms of fibrositis. Diathermy is useful in bringing the affected area under the direct influence of heat, but in the majority of cases, heat applied to the surface appears to be more effective. Ionization applied to the buttock sometimes proves useful, especially in neuritis. The effect is due rather to the action of the current on the tissues than to the drug used. Massage is a valuable method of treatment relieving the deep-seated congestion, restoring muscular tone, removing the products of disordered metabolism, and correcting spasmodic muscular contractions. Massage combined with radiant heat is the most useful

treatment in lumbar and sacro-iliac strain, sciatic neuritis, and fibrositis.

Counter-irritation may be applied with radiant heat, hot bottles, poultices, belladonna plaster, liniment of aconite or tincture of iodine may be applied daily to the line of the sciatic nerve on the skin until the skin is on the verge of blister formation. Aspirin, phenacetin, caffeine and allonal are the most useful analgesic drugs for the relief of pain. In the more resistant cases injection of oxygen usually affords much relief. The technique is easy, harmless and painless. A pneumatic cushion is formed by distension of a wide area around the nerve, due to introduction of oxygen through a hypodermic needle connected by thick India-rubber tubing to an oxygen cylinder. Injection of a salicylic acid solution in doses of 15 to 30 min. (1 in 20 of sterile water) very often gives relief. A preliminary injection of cocaine should be given before the injection is given as this might cause pain afterwards. Acupuncture of the nerve is not performed nowadays, and open operation to stretch and free the nerve from adhesions is a better procedure, which often gives relief in a severe acute attack of sciatica. When the acute stage is over, physical therapy in form of immersion baths with underwater douche massage over the nerve and subsequent manipulation is of value, and the patient should be asked not to make any sudden movement that will stretch the nerve.

Harris advocates an injection of normal saline at the sciatic notch, or the gluteal fold, the dose is 20 to 100 c.cm. and this is preceded by the injection of a few drops of novocaine solution. It is very effective in perineuritis, and particularly when the site of the trouble is in the region of the sacro-iliac joint. Injections of oxygen and even air have given relief in some cases, probably by breaking down adhesions and reducing congestion.

Before treatment is commenced a search should be made for septic foci and when found, these should be eradicated. Metabolic disorders should be corrected on similar lines.

In interstitial neuritis of the brachial plexus either the whole plexus or certain roots only are involved. The site of pain depends on the distribution of the nerves and there are usually no motor, trophic or sensory changes. The pressure due to vertebral diseases, a cervical rib or involvement of glands in the axilla may be responsible for the pain. In brachial neuritis the onset is usually sudden and the pain is made worse by abduction and circumduction of the arm. Tenderness is particularly marked over the upper half of the deltoid muscle as the axillary nerve is usually involved in the inflammation. The arm should always be supported in the abducted position. *Intercostal neuralgia* may be caused by fibrositis of the intercostal nerves or muscles and is generally accompanied by intense acute pain simulating that of pleurisy or by pressure on the nerves by mediastinal growths. In neuralgia of the twelfth thoracic nerve, the pain and tenderness are superficial and

the condition is very often wrongly diagnosed as appendicitis. Similar involvement of the occipital nerve causes severe headaches, especially in the morning with tenderness over the course of the nerve. A true Bell's palsy is due to involvement of the nerve after its emergence from the stylo-mastoid foramen, by pressure of a parotid tumour, or as a result of common cold, etc. Irritation within the buccal cavity is also a frequent cause of facial neuralgia. Radiograms of the teeth will reveal any anomalies and malformations which act as sources of peripheral irritation. The treatment of the above conditions is the same as that of lumbago.

In neuralgia of unsatisfactory blood states, chiefly due to anæmia, the treatment resolves itself into the treatment of the anæmia by suitable hygienic, dietetic and medicinal means. An outdoor life in a bracing climate is the best hygienic treatment in these cases. The diet should include abundance of vitamin-containing foods in which butter and cream should receive a prominent place. Fats seem to be concerned in some very special manner with the nourishment of the nervous system and in the form of butter and cream, they may be freely given to these patients. Alcoholic drinks may be allowed only in moderation. Iron is the best drug in these cases, but the stronger salts, the sulphate and perchloride, are much less efficacious than the citrates and tartrates. The two latter are readily assimilated whereas the former are very apt to upset the stomach. A useful formula is : citrate of ammonium and iron 10 gr., alkaline liquid extract of arsenic 2 min. and watery infusion of quassia to $\frac{1}{2}$ oz., to be taken thrice daily after meals. When the patient improves, the following may be prescribed : citrate of quinine and iron 20 gr., alkaline liquid extract of arsenic 5 min., tincture of nux vomica 4 min. and orange water to $\frac{1}{2}$ oz., to be taken thrice daily after meals. The presence of quinine even in such doses may help to subdue the neuralgia. In prescribing preparations of iron, the bowels should always be kept open ; this is best done by aloes at first because this drug enhances the effect of iron, and later cascara should be given. A daily morning dose of a natural mineral water is also very useful. When the neuralgic pain is severe, drugs having a direct influence upon the pain should be prescribed. A useful prescription, for the purpose, is hydrochloride of quinine 5 gr., dilute hydrobromic acid 20 min., tincture of gelsemium 10 min. and chloroform water to $\frac{1}{2}$ oz., to be taken every 20 minutes till the pain ceases and not more than 4 doses to be taken.

The state of the blood in goutiness is highly provocative of neuralgic pains and so iodide of potassium is very useful in these cases. Sometimes the following may help : salicylate of sodium and phenazone each 5 gr., syrup of ginger 1 dr. and chloroform water to 1 oz., to be taken every 15 minutes until pain ceases, and not more than four doses should be taken. This is a most admirable combination in migrainoid neuralgic attacks to which the gouty are peculiarly

prone. A fruitful and easily overlooked cause of neuralgia, especially in women, is toxæmic condition induced by chronic constipation. Along with the usual treatment of constipation, neuralgia should be treated with phenazone and the salicylate mixture, quinine and gelsemium are to be preferred where the patient is anæmic and emaciated. In them peripheral irritation from septic teeth, tonsils, errors of refraction, etc., should always be borne in mind.

In neurotic women complaining of neuralgia, the best drug to use is belladonna and should often be combined with phenazone. For the relief of facial neuralgia, butyl-chloral is probably the best of all internal remedies. It should be given in a pill of 5 gr. every half hour until the pain ceases and not more than six pills given. It is usefully combined with gelsemium which has a selective influence over cranial neuralgias. Locally, liniment of aconite painted over the painful area, is sufficient to cut short an attack. For vague, ill-defined neuralgic pain, chloride of ammonia 20 gr. combined with tincture of cimicifuge 20 minims is effectual. Acetanilid (antifebrin) is a valuable drug for the relief of neuralgic and neuritic pains. It is better to prescribe the drug cautiously in small doses (2 gr.) for fear of its untoward effects. Apart from morphia, this drug is the most powerful anti-neuralgic inasmuch as it relieves the pains of locomotor ataxy and of other organic diseases of the nervous system. The drug is practically insoluble in water and so is best given in cachets combined either with salicylate of sodium (10 gr.) or camphor monobromate (6 gr.). Morphia is unequalled regarding its effects in relieving intense neuralgias accompanying fevers like influenza and other toxæmias but its prolonged use in recurrent neuralgias is undesirable. In full-blooded individuals, leeching often affords relief in neuralgic pains and this is of particular value where the pain seems to be in or to radiate from the ear.

TRIGEMINAL NEURALGIA. Sigwald in discussing the various methods of treating trigeminal neuralgia, favours section of the trigeminal nerve above the Gasserian ganglion. This however is a serious operation which belongs to the scope of the neuro-surgeon and not the general practitioner and so other methods of treatment have frequently to be relied upon rather than such a severe procedure. Injection of alcohol into the nerve certainly relieves many cases, though it may not cure the condition. Radiotherapy has also had successful results, therapeutic X-rays being directed to the ganglion. Ionization with aconite or with calcium chloride has also proved successful, carried out thrice weekly for a month. A prescription containing aspirin 6 gr., pyramidon 4 gr., opium powder $\frac{1}{3}$ gr. may alleviate the severe pain for a time. Injections of parathyroid extract, insulin and horse serum have also brought about temporary alleviation.

NON-SPECIFIC PROTEIN THERAPY. Non specific protein therapy or protein shock therapy consists essentially of the injection of a protein either in the form of a sterile solution of albumose or a bacterial vaccine by the intravenous or intramuscular route.

Within the last few years this form of therapy has gained considerable popularity. The value of non-specific therapy was empirically established many years ago. Bokenham (1896) reported that diphtheria antitoxin was effective in typhoid and streptococcal infection. Rumpf (1893) treated typhoid patients successfully with pyocyanus vaccine. Koch and Matthes observed that tuberculous patients reacted not only to tuberculin but also to injections of dextro-albumose. Renaud (1911) found that a typhoid vaccine killed by quartz light radiation had a definite therapeutic effect on a number of inflammatory conditions of non-typhoid origin. Kraus and Mazza (1914) reported similar results using *Bact. coli* as well as typhoid vaccine in puerperal infections. Similar instances of success in treatment with purely non-specific proteins, such as Coly's fluid, autoserum, whole blood, milk, intramuscularly and intravenously, have been reported. But the place of non-specific protein in treatment was definitely established as a sequel to Wright's vaccine therapy in 1916. Since then the agents used in the past few years, with the idea of immunizing the patients, are legion. The therapeutic effect produced by these substances, though considered different previously, are now considered to be of the same type. These substances act as non-specific stimuli to the normal immunity mechanism and help to produce the various reactions on which depend the beneficial effects.

The non-specific proteins that have been commonly employed are :—

1. BLOOD AND BLOOD SERA. (a) *Whole blood* either citrated or not may be given subcutaneously or intramuscularly in doses of 10 c.cm. (b) *Normal sera*, human, horse, sheep, ox, goat, etc. (c) *Immune sera*, e.g., human convalescent sera, pneumococcus, streptococcus and dysentery sera, diphtheria and tetanus anti-toxin.

2. PROTEIN SOLUTIONS. (a) *Proteins of animal origin*. Nowadays milk is the chief agent employed, 2 to 10 c.cm. being given intramuscularly twice a week; aolan which is a preparation of milk is often used. Other proteins of this nature are egg-albumin, serum albumin, casein, snake venom, etc.

(b) *Proteins of plant origin*. Nucleic acid and sodium nucleinate are used; the dose is 0.5 gm. hypodermically or intramuscularly in 5 per cent. solution. Other examples are agar-agar, pollen extracts, etc.

(c) *Protein split products*. Proteoses prepared from milk are given daily in doses of $\frac{1}{2}$ to 2 c.cm. of 2 to 10 per cent. solution. Peptone, for the production of shock, is used in 10 per cent. solution in doses of 5 to 10 c.cm. intravenously. Peptones are also used in hæmorrhagic diathesis, paroxysmal hæmoglobinuria, septicæmia and in allergic conditions, for which 5 per cent. solution is given intravenously and 7.5 per

cent. solution intramuscularly in doses of 5 to 40 min. Peptones, e.g., Witte's peptone, are also given by mouth.

3. ENZYMES. Trypsin, amyllopsin and leucocytic extracts.

4. BACTERIAL PRODUCTS. *Typhoid vaccine* in doses of 25 or more million organisms intravenously. *Bact. coli* vaccine 20 or more millions. Coly's fluid for malignant tumours. Malaria inoculation in parasymphilitic condition. Tuberculin has also been used in non-tuberculous subjects.

5. TISSUE EXTRACTS. Spleen extract has been used in hæmopoietic diseases and allergic skin conditions; 5 c.cm. of 40 per cent. solution is given on alternate days for 12 injections. Tumour extracts, autolysates, vascular and muscle extracts are also used.

6. CHEMICALS AND OTHER COLLOIDAL METALS. Gold, silver, manganese, sulphur, iron, platinum, mercury and antimony are used. These substances when employed non-specifically are said to act by breaking down inflammatory tissues with resulting protein absorption. Similarly X-rays, radium, cauterization, diathermy, freezing with CO₂ snow, and ultra-violet light treatment may be considered to be indirect methods of protein therapy.

7. MISCELLANEOUS. Hyper- and hypotonic salt solution, distilled water, glucose, etc.

Character of reaction. Certain focal and general reactions develop during treatment which depend upon a variety of factors, such as age of the patient, nature, duration and type of illness, the choice of protein and the dosage employed. The general and focal reaction is the goal aimed at in non-specific protein therapy, though no satisfactory explanation has been offered as to the manner in which it influences the process of the disease. It seems likely that the mechanism of the reaction is the general stimulation of the whole defensive forces of the body against an irritant introduced in the circulation, and that this reaction in some cases may lead to inhibition or even destruction of the causative organisms of disease. A focal reaction is always desirable, but the best results are obtained when it is slight. It consists of an intensification of any local inflammatory process followed by a diminution until the original condition is reached. Generally within fifteen minutes of the injection chill or rigor may occur, which passes off within half to three-quarters of an hour. A rise in temperature occurs which varies with the patient and the agent employed. When a vaccine is given intravenously, a maximum temperature of about 104°F may be reached in 3 to 4 hours, while with milk intramuscularly the maximum is attained in 6 to 8 hours. Increase in pulse rate and rise in blood pressure are to be expected. On the leucocytes, the effect is a primary leucopenia, probably due to the accumulation of the leucocytes in the viscera; later this is followed by leucocytosis which reaches its maximum in 4 to 8 hours. Very strong stimuli produce long-continued leucopenia followed by hyperleucocytosis. The degree of these reactions has

different significance for different diseases. In cases of chronic diseases, such as arthritis, marked focal and general reactions are indicative of a beneficial effect, while in diseases like asthma or typhoid fever, such reactions will be harmful. *

Following vaccine therapy, headache is quite common. Nausea, vomiting and herpes occasionally occur. The coagulation time of the blood is said to be diminished, metabolism and glandular activity are augmented. The injected foreign protein is said to be removed from the blood stream by the cells of the reticulo-endothelial system.

MODE OF ACTION. The exact manner of action of non-specific proteins is unknown. It has been shown that certain reactions such as rise in temperature, pulse rate, etc., are followed by increased glandular activity and augmentation of metabolism. All these reactions gradually subside leaving the patient in a clinically improved state.

The essential changes observed in the blood after injection of a non-specific protein are. (1) change in the leucocyte count, and (2) antibody changes. Spektorovskaya (1925) found an initial leucopenia in 80 per cent. of cases after injection of non-specific proteins, but from the third to the seventh day a moderate leucocytosis occurred. Other observers have, however, shown that the initial leucopenia is of very short duration and is followed within a few hours, by leucocytosis lasting for several days. Both granular and non-granular leucocytes have been shown to be increased; others found that after injections of proteins, e.g., milk, peptone and typhoid vaccine, an increase in neutrophils occurs, while distilled water produces an increase in mononuclear cell response.

With regard to antibody changes, it has been shown that after injections of non-specific proteins there is an increase in the titre of antibody already present in the serum. But many workers showed that they had no power to increase the antibody titre when this had become steady, but when these proteins are given at the same time as the bacterial antigen, they appeared to increase the anti-body production. The results of these experiments have been summarised by Topley (1929), who states that non-specific stimuli cannot cause the appearance *de novo* of any of the known antibodies in the serum but they can cause an increase in any of the normal antibodies present. They may also cause an increased production of antibodies if given during the early stages of immunization or when the effect of preliminary specific immunization is declining.

Though serological, cellular and other changes occur after injections of foreign proteins the mechanism of cure is still undetermined. Different theories have been postulated to explain the phenomenon. Gay and Claypole (1914) ascribed the beneficial effect to the leucocytosis produced, but it has been observed that the clinical result is not always commensurate with the blood changes. Paltanoff (1915) considered the beneficial effects to be due to thermogenic substances in the proteins

used. Rohonyi (1916) thought that non-specific therapy produced some neutralizing substances against the invading organism. Weichart (1919) attributed the action to a general stimulation of blood and tissue cells, thereby increasing the general resistance and speeding up the mechanism of detoxication, but Dollken showed that it was due to selective stimulation of certain organs, such as the liver, spleen and bone-marrow. Larson (1919) thought that injections of foreign proteins liberate the so-called sessile antibodies into the circulation. Pemberton (1920) considered the effect to be due to increased catabolism of glycogen. Mackenzie and Frahlaner (1927) showed that it acted by the re-awakening of an old immunity that has died away due to lapse of time, to this they applied the term 'anamnestic reaction.' Peterson (1928) believed that the true mechanism of action lies in a combination of several factors, such as, (i) a decreased permeability of cell membrane and hence increased tolerance to intoxication, (ii) cellular stimulation and mobilization of proteolytic enzymes with power to destroy toxic material, (iii) the lymphagogue effect that floods the lymph spaces with plasma rich in antibodies, (iv) increase in the anti-enzymes which makes the proliferation of bacteria difficult. Others have suggested that besides the increased production of antibody, complement, etc., the part played by the sympathetic nervous system and the endocrine glands may not be insignificant.

Therefore it seems probable that this form of treatment is based on rational and scientific foundations. When introduced into the body it assists the reactions which are common to all infections and conditions in which sensitization has occurred, and so enables the individual to desensitize or immunize himself. It is significant in this connection to note that an attack of one disease often has a beneficial effect on another entirely different in origin, from which the patient may be suffering at the same time.

THERAPEUTIC USES. *Infectious diseases* Infectious diseases, e.g., typhoid, tuberculosis have been treated with non-specific proteins. But it should not be used indiscriminately, as in this way, there is chance of converting an otherwise latent infection into an acute one. It is particularly suitable in localised rather than generalised infection and where the disease is of an undetermined nature or where the foci of infection cannot be reached for preparation of a vaccine. When the specific therapy has proved of little value, non-specific therapy may in such cases reactivate the healing mechanism. One or other of the bacterial vaccines or whole blood may be injected in these cases.

Arthritis. Non-specific protein therapy is most commonly employed in arthritis (see page 1251).

Asthma and other allergic conditions. In allergic conditions non-specific therapy has been used with advantage (see page 1232, 1262).

In other allergic conditions such as urticaria and angio-neurotic oedema, localised and generalised pruritus and pemphigus

autohæmotherapy and autoserotherapy have been tried. After withdrawal of blood from a vein, it is reinjected intramuscularly after defibrination, in doses of $\frac{1}{2}$ to 2 c.cm. every 24 hours or less or as freshly separated serum in doses of 2 to 4 c.cm. repeated at 2 to 7 days interval until a dose of 10 c.cm. is reached. In case of urticaria and angioneurotic oedema the best results have, however, been observed with injections of 33 $\frac{1}{3}$ per cent. peptone solution, given at first intradermically for the smaller doses and later subcutaneously. Urticaria papules in children is said to be cured after one or two injections of mother's serum.

Skin diseases. In dermatological conditions non-specific protein therapy has often proved useful. In eczema and dermatitis all methods have been used, but the most frequently employed is auto-sero and auto-hæmo therapy. Turpentine injections also give just as good results. Vaccines (typhoid, staphylococcus and streptococcus) have also been used but less frequently. Psoriasis has been treated with autoserotherapy, auto-hæmotherapy, intravenous vaccines, especially typhoid, milk and its derivatives. This form of therapy has been extensively used in lichen planus, lupus vulgaris, lupus erythematosus, leucoplakia, chronic X-ray dermatitis, etc. The consensus of opinion seems to be that in most of these dermatological conditions, the non-specific agents increase the susceptibility of the lesions to local treatment and so hasten the cure.

Syphilis. All stages of syphilis have been treated with non-specific injections either alone or in combination with specific drugs. Milk injections or a combination of milk and autohæmotherapy have been used in primary syphilis. Tuberculin injections have been used in secondary syphilis, as also typhoid and cholera vaccine, but the results have not been very satisfactory unless drugs are given at the same time. An attack of malaria is also known to influence beneficially cases of syphilis, but it has been found that induced malaria is probably without effect in the early stage while it does good in the later stages. This is especially true in cases of neurosyphilis. Within recent years malarial therapy has been very extensively used in the treatment of neurosyphilis and especially in tabes and G. P. I. The malarial treatment has however some disadvantages; it is always difficult to control the severity of an attack and there has been a certain amount of mortality from this treatment. Injections of typhoid vaccine and tuberculin have also been advocated and the results are said to be just as good both with regard to clinical conditions and their effect on the Wassermann reaction.

Gonorrhœa and its complications. Milk injections have been used with satisfactory results in both gonorrhœal urethritis and its complications. Autoserum has been recommended for gonorrhœal prostatitis and equally good results have been obtained with auto-hæmotherapy. Milk, bacterial vaccines, such as typhoid and *Bact. coli*, have all been used. Apparently it seems that non-specific methods give just as good results

in the treatment of gonorrhoea and its complications as the specific gonococcal vaccines and antiserum.

Other miscellaneous affections have been treated with non-specific therapy. In iritis and gonorrhoeal ophthalmia, milk injections are said to act like a specific remedy. Beneficial results often follow the use of milk in cases of keratitis, choroiditis, retinitis, conjunctivitis, corneal ulcers, etc.

In cases of purpura and hæmophilia where patients give manifestations of a hæmorrhagic diathesis, milk has been employed largely on account of its additional styptic effect. Vaccines of staphylococci and *B. prodigiosus* have been tried in neuritis. The beneficial effects of injections of tumour or bacterial autolysates in decreasing the growth of tumours have been described. Recently non-specific therapy has been employed to cause local vasodilatation in such diseases as Raynaud's disease, thromboangitis obliterans and arteriosclerosis.

MODE OF ADMINISTRATION. The patient should have a liberal carbohydrate meal 2-4 hours before injection, and preferably a feed of glucose one hour before it. He should be in bed during the period of reaction, and allowed to drink plenty of fluids; a small dose of codeine or adrenalin should be given to shorten the reaction and lessen the discomfort.

Injections may be given intravenously, intramuscularly, cutaneously and subcutaneously. Injections are given usually at a distance from the lesion but may also be injected locally around it. These are administered at short intervals of 2 to 4 days, as too long an interval may produce anaphylactic shock. The dose should be sufficient to cause a general moderate reaction.

Contra-indications. Although there is less risk of anaphylactic shock with this treatment than with specific desensitization, there are certain dangers associated with it. Milk is liable to give rise to these symptoms, autoserum and autohæmotherapy are less liable to cause them. The patient who is undergoing this treatment should be in a fairly good state of health. Alcoholism is an absolute contra-indication. In generalised or chronic multiple infections of long duration, or states of exhaustion following prolonged illness where it is impossible to stimulate the fatigued cells, non-specific therapy should not be used. Pregnancy has also been given as a contra-indication, but it may be mentioned that pregnancy dermatoses have been successfully treated. Patients with chronic myocardial changes and advanced arteriosclerosis should not be treated by these methods. Pulmonary diseases, especially tuberculosis, may show focal reactions after non-specific protein injections, and care must therefore be exercised in these cases.

It thus appears that provided certain precautions are taken, non-specific therapy is a safe and useful method of treatment for many diseases. The best results are obtained if it is combined with suitable general or local drug treatment. It is not very important which form

of protein is used, whether autohæmotherapy, milk, or bacterial vaccines, provided the dosage is regulated not to cause too severe reaction.

OBESITY. See page 1051.

CEDEMA. Œdema is a condition in which there is an abnormal accumulation of fluid in the intercellular spaces. Various theories have been propounded from time to time to explain the ætiology of œdema. Fischer holds that œdema is produced by the presence of an excessive amount of water in the tissues when the affinity of the colloids of the tissue for water is increased above normal. Under normal conditions, the tissue fluid is present only as an ultra-microscopic layer of fluid around the cells and according to Fishburg, œdema is produced only when such delicately adjusted dynamic equilibrium between the tissue fluid, the cells and lymph is thrown out of gear. About one-tenth of the water in the body is in the blood and œdema is produced as a result of changes in the blood. Wells holds that œdema is mainly the result of a process of filtration, while the vitalistic school maintains it is mainly the result of secretion. One is a plethoric condition with increased pressure and the other a diminution of protein-contents of the blood in such vessels. Starling held that œdema is due to increased permeability of the capillaries. Peptone and allied lymphogogues act as tissue-poisons and injure the capillary endothelium; the injured endothelium permits more fluid to pass through. Further there was a second class of lymphogogues advocated by Starling which produced a condition of hydræmic plethora and thus caused increased filtration.

According to a recent theory the capillary wall plays only a passive role in the fluid escape. The passage of water and crystalloids in and out of the capillaries is determined by forces on either side of the capillary wall and not by any active function of the latter. Fishburg maintains that increased permeability of capillaries plays a part only in cases where the œdema fluid contains considerable quantities of protein. With all these various theories, œdema may be defined as a condition in which fluid accumulates excessively in the intercellular spaces, in the tissues and in the serous cavities of the body.

Œdema occurs in many diseases and a correct knowledge of the factors responsible for its causation is essential for rational therapy. The common conditions which bring about œdema are increased capillary blood pressure, increased capillary permeability, impaired lymph drainage, decreased colloid osmotic pressure of serum proteins and the specific toxic excretory function of the kidney. The kidneys are said to normally eliminate certain electrolytes and under pathological conditions this eliminative process is interfered with, specially by sodium chloride but not potassium, ammonium and calcium ions. Loeb maintains, however, that the difference between the normal and nephrotic

kidneys is not so much qualitative as quantitative. This quantitative difference is attributed largely to the differences in the serum protein concentration of the blood.

CLINICAL TYPES. *Cardiac œdema.* It is met with in cases of congestive heart failure, where venous pressure is increased, capillary circulation retarded, the tissues suffer from lack of oxygen, nutrition of the tissue cells is impaired and tissue metabolism is interfered with, resulting in an accumulation of excessive fluid in tissue spaces, and lastly it is probably associated with some obstruction to the lymphatic outflow. In cardiac œdema the fluid is shared by all parts of the body. Bolton suggests the origin of the œdema fluid near the cardiac region and the visceral peritoneum. It then gravitates to the lower extremities whence it is partly reabsorbed by the local lymphatics. When the left chambers of the heart are primarily involved as in hypertension, aortic insufficiency or mitral stenosis, œdema appears and limits itself to the pulmonary regions. Facial œdema in cases of heart failure generally indicates a thrombosis of the jugular vein, or congestive renal changes as met with in the later stages of cardiac failure. Prognosis is usually grave in these conditions.

Treatment. The treatment of cardiac œdema should aim at reduction of the venous congestion by means of rest, venesection, pleural and abdominal paracentesis, careful massage, digitalis, diuretics such as diuretin, theocine, novasurol, salyrgan, ammonium chloride, etc., and hydragogue purgatives. Diet therapy includes a low protein diet in early cases and a high protein diet in later stages, when œdema is due to loss of an excessive amount of body protein malnutrition sets in. In early stages, it is always better to stick to a low protein and a high carbohydrate diet with a limitation in the amount of fluid intake. Efficient measures should be adopted early to avoid a later anoxæmia.

Nutritional œdema. In this condition the protein of the blood serum is decreased. The causes are to be sought in a deficient supply to the body of exogenous proteins in the food, excessive loss of protein through urine and from bleeding and lastly from non-absorption of nutritious materials from the gastro-intestinal tract. It is also met with in cases of vitamin deficiency and starvation, in chronic dysentery, in chronic tuberculous enteritis, in sprue, in hookworm infection, in piles, in pernicious anæmia, in pregnancy and lactation, in diabetes mellitus, in chronic alcoholism, in cirrhosis of liver and in cardiac insufficiency. These and other factors, help in precipitating the condition. The ideal treatment in nutritional œdema is to supply an adequate amount of protein in the diet with a restriction in the amount of salt.

Œdema in anæmia. In anæmia the amount of protein in the blood plasma is much diminished. Moreover, associated complications such as the involvement of heart and kidney as seen in pernicious anæmia, are also responsible for the condition. The treatment in these conditions

consists in treating the primary cause and supplying an adequate amount of protein in the diet.

Allergic œdema. In allergic œdemas, different parts of the body are attacked and symptoms too vary in such cases. The treatment in such cases aims at finding the cause of allergy and removing it as far as possible. Calcium and adrenalin therapy is useful in these cases. A small dose of thyroid alternating with ephedrine is able to control it more effectively.

Renal œdema. Here œdema may be generalised all over the body, or limited to certain places where loose areolar tissue predominates. Œdema is due to the renal damage as seen in cases of acute nephritis, nephrosis, and chronic nephritis. In acute glomerular nephritis, owing to the inflammatory changes in the glomeruli, the blood flow through the kidney is greatly reduced resulting in a retention of water, salts and nitrogenous waste products. In later stages the plasma proteins are diminished from loss of albumin in the urine and a condition of malnutrition sets in. In nephrosis, the œdema is associated with massive albuminuria. It is not always possible to attribute the œdema in these cases to a failure of the kidney to excrete salt or water. In such cases factors such as the total amount of serum protein, the hydrostatic pressure in capillaries and the ability of the kidney to excrete various ions should be considered to explain the causation of œdema. The serum protein is always low (being about 4 per cent.) in nephrosis, a disorder in which the kidney also is suffering just as any other part of the body would do. *Epstein's treatment of chronic nephrosis*—Epstein introduced the high protein diet in these diseases to cut short œdema. Epstein believes the effect to be partly due to the specific dynamic action of the protein, which counteracts the lowered basal metabolism in this disease, and partly to increase in the protein content of blood plasma. McLean believes that the reduction of œdema is due to diuresis set up by the large quantities of urea and other non-threshold bodies formed from the high protein diet. Renal functional tests should be performed before putting a patient on high protein diet. Epstein's diet contains: proteins 120 to 240 gm., fats 20 to 40 gm., carbohydrates 150 to 300 gm., giving a total calorific value of 1250 to 2500. Besides this, he allowed 1200 to 1500 c.cm. of water and enough salt to give a certain amount of taste. The articles allowed are lean meat, fish, white of egg, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea, cocoa. He allowed 2 to 3 gm. of protein per kilo. of body weight. Medicinally, Eppinger advocates extract of thyroid, which induces diuresis in these cases, especially in nephrosis.

Neuropathic œdema. This type is often associated with disturbed function of the sympathetic system and is seen in different parts of the body. Ranvier has shown that the nervous system is responsible for the production of œdema in many cases. In paralytic limbs, the absence of

muscular activities retards the removal of lymph, resulting in œdema. Stimulation of vasodilators also causes œdema. The treatment mainly includes physical therapy in the form of massage, electro-therapy and splinting to prevent subsequent deformities, etc.

Lymph œdema. It is seen in cases of filariasis, leprosy, chronic leg ulcers especially those associated with cicatrization, cellulitis, and erysipelas. There is also a congenital and familial form of tropho-œdema known as Milroy's disease. Œdema is often met with after extensive surgical operations, cicatrization and infiltration may play a part in this.

Alkali œdema. It is sometimes seen in alkali therapy of diabetes, gastro-duodenal ulcers, lobar pneumonia, etc. and disappears on the discontinuance of the alkali. Fischer explains it by saying that sodium proteins have a greater affinity for water than calcium or magnesium proteins, and that the sodium salts administered replace the calcium and magnesium in the tissues.

Inflammatory œdema. Injury to the capillary wall plays an important part in the production of œdema. Increased blood pressure, impeded lymph flow, an excessive formation of metabolic products, the asphyxiated condition of inflamed tissues which favours acid formation and naturally increases the avidity for water in the tissues are the factors that influence the œdema in these cases. Oswald says that the permeability of the vessels for proteins is specifically altered in inflammation so that not only the less viscous albumin and pseudoglobulin pass through, but also the more viscous englobulin and fibrinogen.

GENERAL PRINCIPLES OF TREATMENT OF ŒDEMA. *Restriction of diet.* When œdema has set in, control of diet is most important and even in very early cases it may abort an attack. Salt and water are the two important œdema-producing factors in diet which need careful restriction. The daily supply of common salt to dietaries should be cautiously cut down, and to satisfy taste potassium chloride may be substituted instead. The symptoms of salt deficiency appear only when chloride excretion in urine becomes less than $\frac{1}{4}$ gm. per day. The symptoms of salt deficiency are vomiting, headache, pain in the muscles of the legs and irregularity of the rhythm of the heart. Most raw foods including vegetables contain very small quantities of sodium chloride, while milk, cheese, salted butter, salted fish and preserved meat contain larger quantities of this salt. Restriction of fluid intake depends on the integrity of renal functions. If the urine is of high specific gravity the intake of water should be encouraged to avoid uræmia in the long run. The dangers of too great fluid restriction should always be borne in mind.

Diuretics. Water is the best diuretic, but in œdema its intake cannot be encouraged. Volhard advocates the use of water not exceeding an amount of 1500 c.cm. in cases of anuric or severe oliguric patients with acute glomerulo-nephritis, but even this is not generally

accepted. Of the salts reputed as diuretics, sodium salts are contra indicated in cedema and potassium salts are preferable, those commonly used are citrate, bicarbonate and acetate. Strictly speaking, chloride of potassium, having no influence on the acid-base equilibrium, should replace all other salts. The idea of acidity causing diuresis has led to the use of ammonium chloride and calcium chloride, the former acts as a very good diuretic especially in cardiac cedema.

Urea is a very useful diuretic in cardiac cedema and sometimes also in nephrosis. It is given in large doses, three times a day in combination with a suitable corrective to hide its nauseating taste. Before the administration of urea, tests to prove efficient renal functions should be undertaken. Moeller holds that theophyllin by causing an increased transit of fluid and salt from the tissues into the blood stream, acts as a diuretic especially when the kidneys are functioning well. In cardiac cedema, the purines are said to act by their effect on the heart which they stimulate and on the coronary vessels which they dilate. Diuretin or the double salicylate of sodium and theobromine is a stronger diuretic than caffeine. It has a greater action on the heart and the kidney and a weaker action on the nervous system. It is given in doses of 10 gr. three times a day with plenty of water. Taylor advocates its use up to 90 gr. per day to obtain the maximum effect. Theophyllin or theocine is a stronger diuretic, a more powerful cardiac stimulant and it dilates the coronary vessels better. The dose is 3 gr. 3 times a day. Of the mercurial diuretics, the old and famous Guy's pills has not lost its place in the treatment of cardiac cedema. Very recently, other preparations containing mercury have come into use, of which novasurol deserves mention. Because of its irritating action on the intestine and kidneys it has now been replaced by salyrgan, which is equally powerful but less irritating to the bowels. The mode of action of these two drugs as diuretics is not known. Salyrgan is used in cardiac cedema, but it should never be given when renal functions are impaired. Ammonium chloride should be given about 48 hours before the administration of this drug. It can be given either intravenously or intramuscularly in doses of 1 to 2 c.cm. to be repeated every third day. Meyer has given injections of 2 c.cm. of salyrgan directly into the peritoneal cavity in cases of dropsy. He draws about 10 c.cm. of the ascitic fluid from the peritoneal cavity and leaving the needle behind in the cavity, draws 2 c.cm. of salyrgan into the ascitic fluid in the syringe, mixes them up, and then injects the whole slowly back into the peritoneal cavity again. The drug appears to cause no damage to the peritoneum. When given in this way the toxic effects produced by salyrgan are stomatitis, colitis, increase of albuminuria, hæmaturia, moderate fever and circulatory collapse. The double tartrate of bismuth and sodium has also been used as a diuretic in doses of 0.03 gm. injected intramuscularly. Endocrine products such as extracts of thyroid and parathyroid have

also been prescribed for their diuretic effects. In cases, where due to impaired kidney functions, the body cannot get rid of the oedema fluid and is water-logged, recourse can be had to other organs to serve the same function, *e.g.*, the skin and the bowels. Diaphoresis is best effected by means of hot packs, electric baths or a simple hot bath. It is suggested that the elevation of the temperature of the skin might cause a reflex vasodilatation of the kidneys and thereby bring about diuresis. Pilocarpine nitrate is a useful adjuvant in the treatment but it is dangerous in cases of weak heart or oedema of the lung. The administration of purgatives, *e.g.*, saline or vegetable, helps a great deal in draining the fluid from the body in cases of oedema. Recourse has to be taken to surgical operations sometimes, when other measures fail. Drainage of the pleural, pericardial and peritoneal cavities is essential, under strict surgical precautions. It relieves the patient in almost all cases and diuretics are found to act better after such procedures. In cases of dropsy of the lower extremities, the oedema fluid is generally drained by means of Southey's tubes inserted into the most dependent part of the extremities. The fluid led off by rubber tubing is collected in a clear bottle. The tubes are generally retained for 24 hours. Other accessory measures such as sun baths, elevation of the limbs, strapping, pressure bandages, etc., considerably help the treatment.

OPTIC NEURITIS. Inflammation of the optic nerve may develop at any spot in the course of the nerve. It is directly visible by ophthalmoscopic examination only when the optic papilla is involved it is called *neuritis intraocularis* or *papillitis*; when the extraorbital portion of the optic nerve is involved it is called *neuritis retrobulbaris* and this can hardly be detected by ordinary ophthalmoscopic examination. The disease is not always due to a local cause but it generally originates in some deep-seated affection and is often bilateral in development. Of the common aetiological factors responsible for the condition, brain diseases are by far the most common cause of optic neuritis. This they produce either by congestion of the brain or by a direct transmission of an inflammation from the brain to the optic nerve, as in cases of tuberculous meningitis or otitic processes. This increased intracranial pressure causes 'choked disc' due to the swelling of the optic papilla. The diseases of the brain complicated with optic neuritis are partly focal and partly diffuse in nature. The tumours of the brain, abscesses, thrombosis of the sinuses, aneurysms, apoplexies, disseminated sclerosis, acute and chronic meningitis and hydrocephalus afford examples of both the focal and diffuse affections of the brain responsible for optic neuritis. Neuritis also follows malformations and injuries of the skull particularly involving its basal part. Other common causes of optic neuritis are of a constitutional nature such as syphilis, acute infectious febrile diseases, chronic disturbances of

nutrition of various kinds, acute anaemia from sudden loss of blood, poisoning with lead, arsenic, alcohol and iodoform (toxic amblyopia of retrobulbar type). In the tropics, chronic cachexias resulting from long-standing illnesses such as malaria, chronic dysentery, albuminuria, diabetes, tuberculosis very often act as potent causal factors in optic neuritis. Septic foci in teeth, tonsils, accessory air sinuses, acute exanthemata such as measles, small-pox, scarlet fever, etc., acute infectious fevers such as diphtheria, pneumonia, influenza and whooping cough are also responsible for the condition. Disorders of the genital system, pregnancy and lactation in the female sex may also lead to neuritis of the optic nerve. Hereditary optic neuritis (Leber's disease), a retrobulbar type, is commonly met with in the male members of a family about the twentieth year. The disease is bilateral, the vision suffers at first though subsequent improvement is the rule. Ophthalmoscopic examination reveals a normal fundus or a slight blurring of the edges of the disc. Ordinarily, in optic neuritis ophthalmoscopic examination shows evidences of inflammation in the optic papilla, its normal colour is altered and is often mottled with white spots or extravasations of blood; the diameter of the papilla also appears to be greater than normal. The most important feature is the swelling of the papilla, projecting above the surrounding retina and the victim suffers from disturbed sight. The disease runs a chronic course and the prognosis is usually grave as the condition might result in optic atrophy.

TREATMENT. The treatment of optic neuritis is essentially a treatment of the underlying causes. Local treatment is hardly effective and consists in removal of congestion by abstracting blood at the mastoid process, diaphoretic measures, administration of absorbent remedies such as iodide of potassium, oleate of mercury (to be rubbed over the nape of the neck). To alleviate pain, aspirin and its derivatives may be prescribed. Surgical procedures such as trephining the skull, should be early resorted to before the vision is lost, in cases of increased intracranial tension. Vision often improves after the operation. Measures to promote general health should always be taken in hand early. In retrobulbar neuritis, treatment should be directed towards the eradication of septic foci of the mouth and nasal sinus. The eyes should be guarded from bright light and kept at rest by the use of mydriatic drugs. Herbert Fisher suggests that hereditary optic neuritis is due to transitory changes in the pituitary body often associated with physiological changes in sexual life and so endocrine therapy with thyroid and pituitary is of great benefit in these cases.

ORGANOTHERAPY. Formerly all organic correlations were assumed to be nervous, but now it is known that various body functions are not controlled by the nervous influences alone, but also by the chemical substances that pass from the tissues into the blood stream. To such

substances the name of 'hormone' or chemical messenger is given. The term hormone (Greek : *hormao*—I arouse) was coined by Starling, but Schafer pointed out that the type of action was not always one of stimulation, and he suggested the word 'autocoid' (Greek : *autos*—self, and *akos*—a drug). Such substances are divided into two classes, 'hormone' that stimulates and 'chalones' that depress activity. This classification, however, has no wide-spread acceptance. 'Incretion' is another term which is now accepted to denote the internal secretion.

Brown-Sequard impressed the medical world with the view that all glandular organs, whether they are with or without ducts, may give off to the blood, substances that are necessary for the welfare of the body as a whole. These include the ductless glands such as the thyroid, the parathyroid, the thymus, the hypophysis, the epiphysis and the adrenals, along with others which elaborate both an external secretion that escapes through a duct and an internal secretion that enters the blood. To the latter group belong the pancreas, the liver, the duodenal and gastric mucosa, and the sex glands.

The normal functions of the glands are only partially understood, and most of our knowledge has been gained by experimental physiology and clinical medicine. The functional abnormalities have been considered to result from insufficient (hypo-function) or excessive glandular activity (hyper-function). This is borne out by the fact that symptoms are relieved by administration of glandular products or by the successful transplantations of the gland in question or in the other cases by operative removal of a part of the gland. But there remains yet another type of clinical condition which does not fall clearly either into the group of hypofunction or hyperfunction. The cause of this aberrant type (dysfunction) is not clear. Possibly it is due to the complex structure of the gland and the different physiological properties of the different parts. Not only the quantity, but also the quality of the incretion may undergo variation and give rise to the clinical condition which represents a mixture of the effect produced by alteration in the component elements elaborated by the gland.

Our knowledge of the pure physiology of the endocrine glands does not help us to get over the difficulty that exists in the application of these principles to the applied science of organotherapy. The existence of the intimate relationship of the various glands and their relation to particular function has been revealed and the obstacle to the furtherance of rational organotherapy has been to a certain extent removed. It has now been demonstrated that the pathological lesions of the individual glands cause some disturbance in the functional relation of other glands, the so-called 'pluriglandular syndrome.' A perfect physiological balance is normally preserved by the proper distribution of harmony and antagonism between the functions of the various glands. The hormones are present in the body to be utilised when occasion arises. Thus a sudden call for increased energy is answered to by the adrenals

and to some extent by the thyroid. The growth of the body requires the action and interaction of many internal secretions, the thyroid, pituitary, thymus, suprarenals, gonads and digestive glands. With reference to the general effect upon metabolism, growth and development, the glands may be classified into two generally opposed groups.

1. *Acceleratory* (katabolic-dissimilatory):—Thyroid, hypophysis (posterior lobe), chromaffin tissue (suprarenal medulla) and sex glands.

2. *Retarding* (anabolic-assimilatory):—Parathyroids, hypophysis (anterior lobe), adrenal cortex, intestinal glands, thymus, pineal, and pancreas (insular part).

In general, the first group stimulates the action of the sympathetic system (sympathicotrope) and the second inhibits it (vagotrope). Of the particular relationship existing between glands and their combined action in functional activity, the following seems fairly well established as a result of experimental physiology and clinical investigations. Definite relationship has been shown to exist between thyroid-pituitary, thyroid-gonad, thyroid-adrenal, thyroid-thymus, thyroid-pancreas, pituitary-adrenals, pituitary-gonad, pituitary-pancreas, adrenal-gonad, adrenal-pancreas, adrenal-thymus and gonad-thymus.

Disturbed physiology in one endocrine gland produces functional and anatomic changes in one or more of the other glands. It has been shown experimentally that excision of one gland often gives rise to secondary changes in other glands. Thus, for example, an increase in the anterior lobe of the hypophysis is observed after thyroidectomy. Graves' disease is nearly always accompanied by menstrual disorders in females and often loss of libido in both sexes. Damage to the cortex of the adrenals produces an increased metabolism by stimulating the thyroid.

The manner by which the internal secretions bring about their characteristic effect, may be described as a direct action on the cell metabolism and through the medium of the autonomic nervous system. The first mode of action may be general and affect the metabolism of all the cells (e.g., thyroid) or specific and affect only one type of cells (e.g., pituitary). The second mode of action is through the autonomic nervous system and this probably accounts for the great majority of internal secretion effects. Through this channel it helps to maintain an efficient co-ordination of the most complex animal organism. The balanced action of the two parts of the autonomic nervous system—the sympathetic and the parasympathetic—is intimately bound up with the internal secretion and is of utmost importance in interpretation of the various clinical syndromes.

The branch of therapeutics in which certain diseases are treated by extracts from endocrine glands is known as organotherapy or opotherapy. It is a very ancient practice and was for very long on an empirical basis. A large proportion of modern organotherapy is, however, devoid of any scientific basis, but the modern development and

steady additions to our fundamental knowledge of the subject make it possible to offer some explanation as to their mode of action. The mechanism of modern organotherapy may be as follows:—

(a) *Substitution*. In cases of lessened or faulty secretion of a gland, a specific substance formed by the gland in normal physiology is introduced into the system. The results obtained cannot be wholly explained on a substitutional basis, probably some other factors are at play. Insulin therapy in diabetes and ovarian therapy belong to this group.

(b) *Homostimulation*. This valuable mode of action was originally postulated by Hallion and is usually referred to as 'Hallions Law.' "The extract of an organ administered in suitable amount has an elective stimulating action on the functional activity of the same organ in the patient to whom it is administered." Many clinical evidences may be put forward in support of it, but the extent of its applicability is still undefined. After administration of a glandular product, there is at first a stimulation to increased functional activity of the homologous organ and secondly, there is actual rebuilding of the affected organ. Thyroid therapy and pituitary therapy belong to this group.

(c) *Utilisation of a product for its physiological influence*. In this form of therapy, advantage is taken of the distinct physiological and pharmacological action of certain gland products. There is no idea, in this form, to obtain any profound endocrine (hormazone) effect. Epinephrine may be used to stimulate the heart's action or cause vasoconstriction in cases of shock.

(d) *Reciprocal action*. This is based upon the intimate inter-relationship that exists between the different endocrine glands. The gland which plays the most important part in the clinical picture is not only dealt with in this therapy, but also other glands either compensatory or antagonistic, which act as an intermediate factor in bringing about the effect.

In this connection it may be mentioned that there is another aspect of the mode of action and that is known as 'antagonistic action.' Excessive secretion of one gland is neutralised by extract of another, assumed to be antagonistic. This adjustment to rectify a faulty hormone balance is very important in the field of organotherapy.

(e) *Empirical*. It is based upon the clinical observation that certain gland products or their combination have a favourable action upon some clinical syndrome. Our limited knowledge about the ætiology and pathology of these conditions and their relationship to the different endocrine glands, is responsible for the lack of any scientific explanations.

•The failure resulting from the use of a single gland product was in some cases due to the fact that the fundamental fact of endocrine inter-relationship was not taken into account in therapy. "Uniglandular organotherapy had its rise when clinical and experimental observation disclosed the phenomena which result from alteration or extirpation of

one or another glandular element, failing to take account for the most part of the anatomical and physiological connections between these elements. But when the complete functional unity and intimate biological connection came to be understood, their morbid manifestations ceased to be looked upon as due to separate factors and treatment became influenced by their physiological inter-relation, the only method of dealing fully with their functional insufficiency." Endocrine diseases are now recognised as pluri-glandular syndromes and successful results are obtained in cases by mixed organotherapy, where one gland fails to produce any improvement. Thyroid-ovarian medication in ovarian insufficiency is an illustration.

MODE OF ADMINISTRATION. The most popular method of administration is by the oral route. The hormones as chemical compounds pass through unaffected by the enzyme action although in some cases they have been known to undergo oxidation, *e.g.*, epinephrine. The hormones as a general rule are simpler bodies than the proteins; they crystallise and dialyse freely. They withstand boiling and, according to Abderhalden, are not destroyed by the action of the digestive enzymes. For those cases where it is apprehended that some destruction may take place in the stomach or intestine, the sublingual method of administration may be resorted to. Subcutaneous, intramuscular and intravenous routes are also resorted to in some cases, but they have limited scope, for the advantages claimed in their favour, *viz.*, the rapidity of action, do not apply in this case, for organotherapy has rarely been applied for treating emergent cases. Parathormone and cortical extract, however, have been used parenterally to obtain speedy effects.

The following are some of the endocrine glands which have been widely used in the field of organotherapy. It is not an inclusive list, but some of the better known preparations are mentioned.

THYROID GLAND. It is most widely used in the therapeutics. Sajous outlines the general field of thyroid therapy as follows:—

(1) In diseases due to slowed destruction of toxic waste products of body metabolism, as shown by its action in tetany, epilepsy, eclampsia, disorders of menopause, asthma, etc. (2) In diseases due to lowered general nutrition of all tissues including the bones, *e.g.*, cretinism, myxoedema, ricket, osteomalacia, etc. (3) In diseases due to lowered nutrition of the muscular elements, including the skeletal and vascular muscles, *e.g.*, adynamia, neurasthenia and myasthenia. (4) In all cases in which the processes of repair or absorption are deficient, *e.g.*, in delayed union of fractures, bone necrosis, etc. (5) In infectious diseases, owing to increase of auto-intoxication, thyroidase, and phagocytes, *e.g.*, in early stages of tuberculosis, typhoid fever, etc.

In certain skin diseases, characterised by a thickened, scaly and dry condition of the dermis, as well as in others, *e.g.*, dermatitis herpetiformis, prurigo, psoriasis and chronic eczema, thyroid therapy is very efficacious.

Preparations. *Thyroxin* is the crystalline autocoid of the thyroid gland. It is not the essential hormone of the gland and has not replaced the gland substance for therapeutic purposes except in the treatment of obesity. It is official in the U. S. P., the average dose is 0.5 mgm. (1/12 gr.). *Thyroid siccum* is a powder prepared from fresh and healthy glands of the sheep. No standard of strength is given. The dose is 0.03 to 0.25 gm. ($\frac{1}{4}$ to 4 gr.). For infants 1/20 gr. may be given thrice daily. In cretinism the dose may be larger. *Elitran* is prepared by the Bayer laboratories and is a particularly potent form of dry thyroid containing as much as one per cent. of iodine. It is used in tablet forms, each one equivalent to 25 mgm. (2/5 gr.) of dry thyroid and may be given in corresponding doses.

The milk of thyroidectomised goats, the serum of thyroidectomised sheep and thyrolytic serum, have also been used with the object of neutralising the excessive and abnormal secretion, to which the unpleasant symptoms of the disease are believed to be due.

PARATHYROID GLAND. The main function of this gland is to regulate the calcium metabolism and to increase the ionisable calcium content of the blood. The glandular product is given in small doses and with good results in all cases of muscle irritability, e.g., in chorea, epilepsy, spasmophilia, tetany, etc. Its use has been advocated in sprue with simultaneous administration of calcium. As it mobilises the calcium from other tissues, mainly the bones and muscles, its use in rickets is contraindicated. Extract of glands, freed from the calcium raising factor and injected into human beings suffering from carcinoma has been reported to have caused some improvement in the condition.

Preparations. *Desiccated parathyroid gland.* Tablets containing 1/20 gr. (0.003 gm.), 1/6 gr. (0.01 gm.), $\frac{1}{4}$ gr. (0.016 gm.) and $\frac{1}{2}$ gr. (0.03 gm.) are obtainable. The average dose is 1/60 gr. (0.001 gm.) to $1\frac{1}{2}$ gr. (0.1 gm.) thrice daily. *Parathyroid extract liquid.* The potency of the extract is estimated by the rise in calcium in blood serum of dogs. It is used in cases where parathyroid glands have been removed by mistake. Injections prove curative. *Parathyroid hormone* or 'parathormone' is an aqueous solution of the active principle of the parathyroid glands of cattle. It is standardised physiologically on the basis of its calcium-raising property. It is specific in tetania parathyreopriva and in other conditions in which there is deficiency of serum calcium. The dose is 20 to 30 units given intramuscularly (one unit is one-hundredth the amount required to raise the serum-calcium of a dog weighing 20 kilo. to 5 mgm.).

Ellixir parathyroid with calcium lactate contains 1/20 gr. of dried parathyroid gland and 3 gr. of calcium lactate in 1 dr. of the fluid. The dose is 1 dr. increased if necessary.

ADRENAL GLAND. It consists of two portions, the cortex and the medulla. Each contains a separate hormone; extract of the medulla is

known as adrenalin, while the exact nature of the hormone of the cortex is still under investigation. Medication by means of the medullary substance as well as with the whole gland has not been very successful; the hormone alone has got some therapeutic application. Adrenalin is mainly used as a vaso-constrictor as well as to maintain the normal tonus of the body. Another very important use of adrenalin is to relieve an attack of bronchial asthma, where it acts by causing the muscles of the bronchioles to dilate. Its use as a restorative during surgical shock and in the treatment of anaphylaxis is well-known.

The active extract of the cortical substance has been largely used in restoring the adrenal function in Addison's disease. Other conditions have also been treated with this, *e.g.*, post-diphtheritic asthenia, severe vomiting, etc. Adrenal cortex has also been tried in cancer but no encouraging results have been obtained.

Preparations. *Suprarenal gland*, dry, has got insignificant therapeutic value. The dose is from $\frac{1}{2}$ to 3 gr., three times a day. *Adrenalin* (synonyms—epinephrine, suprarenin, adrephrine) is an active principle of the suprarenal glands. It is best prescribed alone in solution as it is oxidised rapidly, especially in neutral or alkaline solution. The dose is 1/600 to 1/120 gr. or 0.0001 to 0.0005 gm. *Liquor adrenalin hydrochloride* contains one part of adrenalin, five of chloroform, nine of sodium chloride, three of dilute hydrochloric acid, and distilled water up to 1000. It is used either locally on the mucous membrane or by injection. After oral administration it is largely destroyed in the gastrointestinal tract. The dose is 2 to 8 min., subcutaneously. For resuscitation in cardiac arrest, intracardiac injection of adrenalin is very efficacious; still-born infants have been known to respond to adrenalin by intracardiac injection. *Suprarenal cortex*, desiccated, has been tried experimentally on the grounds that the cortex has a function distinct from the medulla. Dose, 2 to 5 gr. thrice daily. *Cortical hormone*, has been prepared free from adrenalin. It is issued under the name of 'eucortone' or 'cortin'. It is a watery solution of which 1 c.cm. contains the activity of 30 gm. of fresh cortical tissue. The dose is 10 to 20 c.cm. intravenously or subcutaneously in divided doses. Addison's disease responds well to this treatment.

PITUITARY BODY. The two lobes of the pituitary have distinct functions. Extract from the posterior lobe has been found to possess certain definite properties: (1) The pressor property which has the stimulant effect on the muscle of the blood vessels. (2) The oxytocic property, which has a stimulant effect on the muscle of the uterus. (3) The antidiuretic property, which has the power to delay the excretion of excess of water taken by the mouth. (4) The power to increase intestinal movement. Part of the antacid secreted by the anterior lobe is necessary for the normal growth and part for stimulating the ovaries into activity. Zondek considers the sex-stimulating antacid to be of a dual nature; one known as 'Frolan A' which influences the ripening of

the follicle and the other 'Prolan B' influencing the formation of corpus luteum. This factor is utilised in the Zondek-Aschheim test for pregnancy.

The general indications of pituitary therapy have been given by Bell:—(1) For pressor effects on the circulatory system, the uterus, the alimentary tract the urinary system and the spleen. (2) For supplementary effects. (3) For antagonistic and metabolic effects.

Pituitary preparations are particularly valuable in the field of gynaecology. In the treatment of amenorrhœa, dysmenorrhœa, menorrhagia, metrorrhagia, menopausal disorders, for the induction of labour and in cases of sub-involution and uterine hæmorrhage, pituitary extract is of potent value.

Preparations. *Pituitary body dried* (entire gland) has been employed to improve metabolism, to raise arterial tension, to increase diuretic action and improve metabolism. The dose is 1 to 3 gr. *Pituitary substance, dried* (ant. lobe) has been used to stimulate growth and in certain types of obesity. It is given in 1 to 4 gr. doses. *Pituitary substances, dried* (posterior lobe) is used in exophthalmic goitre, acromegaly and to relieve cardiac dilatation. It is also efficacious in intestinal paresis, diabetes insipidus and enuresis. Dose is 1 to 4 gr.

Liquid pituitary preparations of: (a) *Entire gland.* This has been tried in certain types of acromegaly. The dose advised is $\frac{1}{2}$ to 1 c.cm. intramuscularly; (b) *Anterior lobe.* In children with retarded growth this has been used with some evidence of benefit, but it is believed that no active principle from the anterior lobe can pass into the aqueous extract. The dose is 1 to 2 c.cm.; (c) *Posterior lobe (pituitary extract or liquor pituitary).* It is a sterile solution containing the active principle of the posterior lobe of the gland of ox. It has a special action on the uterine muscle and is used to hasten a sluggish labour. It should not be given at the first stage of labour when the os is not fully dilated or when there is some mechanical obstruction. Dose is $\frac{1}{2}$ to 1 c.cm. (1.0 c.cm. of the solution should contain 10 units, i.e., 3.5 per cent. extracts of the fresh gland). The main use of this property is to ensure that the uterus remains contracted after the delivery of the child.

The oxytocic and vaso-pressor principles of the posterior lobe have been separated as stable water soluble powders. *Pitocin* (formerly known as oxytocin) is the oxytocic principle, standardised to the oxytocic activity of the U.S.P. Pituitary solution (10 units per c.cm.). It is also available in such forms as Neo-infundin or Orasthin.

Pitressin is an aqueous solution of the pressor-diuretic-oliguric fraction standardised to correspond to double the pressor activity of the U.S.P. Pituitary solution (20 units per c.cm.).

PANCREAS. The pancreas consists of two types of tissue—the acinar, secreting the pancreatic juice containing the digestive enzymes and groups of cells known as 'Islands of Langerhans.' The latter are proved

to contain a substance which circulating in the blood stream, prevents an undue amount of glucose from accumulating in this fluid and also lowers the blood sugar and diminishes or abolishes excretion of sugar in urine in diabetic subjects. To this the name '*insulin*' has been given. Besides the supply of these two secretions, the pancreas has other functions. The German workers have extracted a circulatory hormone, while another substance described as a hormone and called 'vagotonine' has been isolated by Santenoz and his associates. The action of the latter is complementary to that of insulin.

In certain forms of severe glycosuria pancreatic preparations are particularly valuable. For invalids, aged persons and those suffering from weak digestions, preparations of pancreas may be employed, by which the food may be partially or wholly digested previous to administration.

Preparations. *Pancreatin* is a cream-coloured amorphous powder, consisting principally of amylase, trypsin and lipase. It is partially soluble in water. It digests albuminoids and converts not less than 25 times its weight of starch into soluble carbohydrates. The dose is 2 to 4 gr. *Liquor pancreaticus* is used in doses of 1 to 2 dr. in water with meals, to aid intestinal digestion. It contains amylolytic, proteolytic and milk-peptonising properties of the pancreas. *Trypsin* changes proteins into peptones in alkaline media. It is prepared commercially in the form of whitish powder and one part can peptonise about 100 parts of coagulated egg albumin in $1\frac{1}{2}$ hours. The dose is 8 to 20 gr. *Padutin* is a solution of the circulatory hormone from the pancreas. It is used in such circulatory disorders as arterial spasm, Raynaud's disease and hyperpiesis. Dose, one or more injections daily. *Insulin* is of great value in glycosuria. On injection it converts glucose into the active form and if given at proper intervals blood sugar is maintained at normal level and urine remains free from sugar and there is a quick restoration to normal metabolism. The commercial insulin is composed of three substances, the true pancreatic hormone A, the anti-insulin B and co-insulin C. It is available in the form of aqueous extracts and crystalline insulin. Insulin in solution contains 20 units per c.cm. and tablets of insulin hydrochloride are each equivalent to 10 units. The Public Health Committee of the League of Nations lays down the unit of insulin as one-third of the amount of material required to lower the blood sugar of a 2 kg. rabbit which has fasted for twenty-four hours, from the normal level (0.118 per cent.) to 0.045 per cent. over a period of five hours. The usual dose is 5 to 100 units which can be varied according to the need. The details of the use of insulin in diabetes have been described on page 1447. Besides this above-named condition insulin has also been used in cases in which malnutrition is the outstanding feature, in exophthalmic goitre, hyperthyroidism, vomiting of pregnancy, skin diseases, etc., with encouraging results.

SEX GLANDS. The sex glands are of very great importance to normal health, but they differ from other endocrine glands in that they are not

essential to life. Their main functions are in reproduction, but in addition to these, the sex glands exert an influence upon the growth and development of the body, both physical and mental, and in the female in the process of menstruation.

TESTES. These contain two kinds of cells, the spermatogenetic and interstitial. The first one is responsible for the production of spermatozoa while the interstitial cells also known as 'Leydig cells' give rise to an internal secretion. This hormone is responsible for the general bodily development between the ages of twelve and twenty, but there is evidence also that diminished formation may lead to decay in old age. Preparations from this organ are widely used in the treatment of sexual neurosis, impotence and as a general tonic in old age. Orchic extracts have also been recommended in certain toxic dermatoses and in psoriasis. Transplantation of the testes (Voronoff's method) is supposed to cause rejuvenation and has been tried on the continent. Another method to combat senility is the ligation of the vas deferens (Steinach operation). The idea is that after ligation, there is atrophy of the glandular cells and a subsequent proliferation of the interstitial tissue, which can secrete more testicular hormone and produce the effect desired. The results of both these operations have not been satisfactory.

Preparations. *Orchic substance* is the desiccated product of the gland and is given in doses of 2 to 5 gr. three times a day.

Liquor testicularis (syn. orchidin, testiculin) is prepared from testes of animals by maceration with glycerine. The usual dose is 15 to 30 min., hypodermically or by mouth. Hypodermic injections in doses of 1 c.cm. twice weekly for 6 to 9 doses have good results in cases of loss of virility and general weakness. *Testogan* is a preparation of the hormones of the reproductive gland and of the glands of internal secretion. It is suggested for use in impotence in doses of one tablet three times daily after meals.

PROSTATE GLAND. There is no definite evidence that the prostate has an internal secretion. The association of neurasthenic manifestation with chronic prostatic disorders has led us to believe that probably this gland has some control over the nervous system and with this idea in view a preparation from this gland has been used in the treatment of neurosis. Dose is 1½ to 3 gr. two to three times a day.

OVARY. Like the testes, the ovaries have an internal secretion which in addition to the reproductive function, is responsible for the development of secondary sexual characteristics in the female. Marshall postulated that the ovary produces three factors:—(1) a factor governing development of the accessory organs of reproduction and of the secondary characters, (2) a factor concerned with oestrus (or menstruation in human beings), and (3) a factor controlling pregnancy. Three different hormones have been isolated from the ovary—oestrin (theelin or folliculin), corpus luteum hormone (or progestin) and interstitial hormone. *Oestrin* is mainly used as a means of curing sterility and amen-

orrhoea or as an agent to assist in inducing labour at the end of pregnancy. *Corpus luteum* may be employed in controlling the nausea of pregnancy or habitual abortion without demonstrable cause. Interstitial hormone causes a secretion of the posterior pituitary lobe.

Preparations. *Ovarian extract* is used in dysmenorrhoea, menorrhagia and for climacteric ailments. The dose is 1 to 3 gr. *Ova-mammoid compound* capsules contain 1 gr. each of ovarian extract and mammary gland extract. It is used in neurasthenia, hysteria, insomnia, amenorrhoea and dysmenorrhoea. *Theelin* is the ovarian follicular hormone issued in 1 c.cm. ampoules for intramuscular injection. It is standardised by the Doisy method and its potency is expressed in terms of rat units, being the amount of hormone necessary to induce oestrus as judged by vaginal smear. It is indicated for the relief of the subjective disturbances of the menopause, functional amenorrhoea, oligomenorrhoea, functional sterility, etc. Dose is 1 to 2 c.cm. daily or on alternate days. *Corpus luteum* is prepared from the inert substance of the ovaries and desiccated. Extracts of corpus luteum are found useful in neurasthenia in women in difficulties arising at the menopause, and in conjunction with thyroid or pituitary for incomplete development. The usual dose is 5 gr. thrice daily. *Agomension* is a preparation of early corpus luteum of the cow. It is used in doses of 1 to 3 tablets each 1/3 gr. thrice daily and is found to be of some efficacy in retarded sexual development, genital hypofunction, etc. *Sistomensine* is an extract of the hormone from older corpus luteum. It is said to regulate and stabilise menstruation and is used for menorrhagia, etc. The usual dose being 1 to 2 tablets thrice daily.

Progestin. It is the corpus luteum hormone carefully standardised by its proliferational activity in the immature rabbit uterus which has been previously treated with oestrin. It has been found to be of particular value in the treatment of habitual abortion, the rationale in such cases being to produce a type of endometrium suitable for the nidation of the fertilised ovum, and to inhibit the spontaneous activity of the uterine muscle and its response to the oxytocic principle of the pituitary gland, thus forming the quiescent uterine muscle necessary for the retention of the developing foetus. It is issued in ampoules containing two rabbit units for intramuscular injection.

PLACENTA. The chorionic epithelium of the placenta is supposed to have an action similar to that of the ovaries and during the period when the ovarian functions are in abeyance, the placenta may take up its work to some extent. The placenta is very rich in female sex hormone and its extract stimulates the development of mammary gland and uterus. The human placenta contains at least three hormones (1) the sex hormone, *oestrin* (now known as theelin); (2) an oestrogenic hormone known as *emmenin* and (3) the anterior pituitary-like substance. Of these three only oestrin is obtainable from the placenta of pig or cow.

Preparations. There are various preparations in the market made from the placental hormone which have been used in utero-ovarian hypoplasia, sterility, amenorrhœa, etc. *Oestrin* is a solution of the œstrus-producing hormone (B. D. H.). *Emmenin* has encouraging results in the treatment of dysmenorrhœa; the equivalent of 25 gm. of placenta is given daily for 17 days increased up to 75 gm. daily during the week preceeding menstruation and discontinued with the onset of the flow.

MAMMARY GLAND. The mammary glands have not been shown to possess any hormone but it has been suggested that the activity of the gland during lactation assists in the involution of the uterus. Some authorities hold that extracts from the mammary gland are capable of stopping excessive menstrual loss, while others think it inactive. Mammary gland tablets contain 2 gr. of desiccated glandular tissue from the udder of cows. These have been used in the treatment of uterine congestion, fibroid tumours and in menorrhagia in doses of 5 to 15 gr. thrice daily.

THYMUS GLAND. The thymus is a gland which is essential during the first decade of life. Basch concludes that the thymus gland is not indispensable to life, but that it exercises a transitory function during the earlier months of life when processes of growth and calcification of bone are most active. The therapeutic uses of the thymus gland are largely empirical and are based upon the idea of partial antagonism and partial synergism between the thyroid and the thymus. It has been used in various conditions, e.g., infantile marasmus and atrophy, exophthalmic goitre, rickets, but with little benefit. Its use in deficient development and defective bone formation in infants may have some value. Extracts of the thymus have been utilised by some observers in the treatment of psoriasis with successful results.

Preparations. *Thymus gland*, desiccated. One grain of this powder represents 5 gr. of fresh gland. It has been used in defective nutrition in childhood, hæmophilia, anæmia and various other conditions. The dose is 3 to 10 gr.

Liquid extract of thymus gland. Dose is $\frac{1}{4}$ to 2 dr. *Thymocrin* is a solution from the thymus of calves. Each cubic centimeter is equal to 42 gr. of the fresh tissue. It is used in psoriasis in doses of 1 c.cm. every day or on alternate days.

PINEAL GLAND. The function of this gland is not well understood. It is supposed to be concerned in the growth and development of the sex organs and of somatic growth in general. Extract of the pineal gland has been used mainly for backward children and apparent benefit sometimes follows in cases of mental deficiency with no physical stigmata of degeneracy. The desiccated gland substance is manufactured from the pineal glands of young bullocks. It is administered alone in tablets or in powder form or may be combined with other gland products. The dosage is from 1/20 to 1/10 of a gr.

DUODENAL AND GASTRIC MUCOSA. Bayliss and Starling in 1902 demonstrated the internal secretion of the duodenum and showed that an acid extract of the duodenal mucosa when injected intravenously provoked profuse pancreatic secretion. The active substance of this extract is known as secretin and is occasionally used in therapeutics as a stimulant to the pancreatic external secretion when this is deficient.

The successful use of desiccated stomach in the treatment of pernicious anæmia points to the presence of an anti-anæmic factor in the gastric mucosa. The British workers named this substance as hæmopoëtin and Americans call it addisin. Desiccated and defatted stomach substance has produced satisfactory hæmatopoietic remission. The effect on the reticulated erythrocytes and mature erythrocyte counts is generally very encouraging.

Preparations. *Liquid extract of duodenal membrane* (syn. *secretin*). Extract is prepared from duodenal membranes of pigs, the strength being 1 min. = 1 gr. of fresh mucous membrane. It is used in all forms of pancreatic insufficiency, where true organic changes have not taken place. The dose is 5 to 20 min. *Secretogen elixir* is a proprietary preparation containing pyloric prosecretion and duodenal secretin. It is generally used in faulty digestion of starch with fermentation and flatulence. The dose is 1 to 2 dr. *Desiccated stomach* or *ventriculin* is prepared from hog's stomach and is obtainable in vials containing 10 gm. The dose is 15 to 30 gm. per diem in water=approximately 300 gm. to 600 gm. fresh material. *Extomak* (Benger). The usual dose is 25 to 30 gm. daily in three portions (25 gm.=100 gm. of fresh whole stomach).

SPLEEN. No hormone has as yet been isolated from the spleen, and any treatment with splenic extract is empirical. It has been used in anæmia, tuberculosis, myxœdema, etc. Calcium metabolism is stated to be stimulated by spleen.

Preparation. *Spleen substance*, desiccated, is prepared from pig's spleen, 1 part representing 5 of fresh spleen. The dose is 5 to 10 gr. (0.3 to 0.6 gm.). *Splenex* is a liquid extract of spleen substance, 4 oz. is equivalent to 2½ lb. of raw spleen. The dose is ¼ to 1 tablespoonful daily for 3 weeks, with a week's interval between courses. *Hormonal* is said to be a solution of the peristaltic hormone prepared from cow's spleen. It is used in the treatment of constipation. It is given by intramuscular or intravenous routes in doses of 15 to 20 c. cm.

LIVER. The liver has not as yet been classed as an endocrine gland although with regard to its mode of action in the treatment of pernicious anæmia it has been suggested that the liver secretes a hormone necessary for the maturation of red cells in the bone marrow. The use of liver preparations and extracts in pernicious anæmia has been dealt with under anæmia.

EXTRACT OF MUSCLES. Within recent years this has been extensively used in the treatment of cardiac and circulatory disturbances, e.g., angina pectoris, intermittent claudication and other allied conditions.

The exact nature of the active principles is not known, but it is clinically evident and confirmed by physiological experiment that the extract acts as a powerful depressor. It is well established that in active muscle, some substances (metabolites) are present which are responsible for increased blood supply during exercise and these probably form the active principle of the muscle extract. They may contain adenosine, but physiological experiments indicate that they are not likely to be identical with it. •

The extract is given by intramuscular injection so as to make it potent by deamination in contact with the muscle tissue, the usual dose being 1 c. cm. daily. *Lacarnol*, an extract of heart muscle has been used in true angina pectoris with some benefit. *Myoston*, *eutonon*, *kallikrein*, *angioxyl*, etc., all have essentially the same action, but their precise use and limitations have not been accurately determined.

A few minor glands and organ that remain to be considered are not very important. In most cases the endocrine nature of these is doubtful and there is no evidence at present in support of the efficacy of any of these substances in the realm of organotherapy. The spleen, the kidneys, the heart, the mammary glands come under this group and their role in this branch of therapeutics is purely speculative or empirical.

ORIENTAL SORE. See leishmaniasis, page 1403.

OSTEOMALACIA. This is a chronic disease usually affecting females, characterised by decalcification of bones resulting in bending, fracture and other deformities. It is more common in women than in men and occurs usually during pregnancy or when the diet is deficient in calcium and phosphorus. Defective hygienic conditions and lack of proper nutrition are said to predispose and the disease is not exclusively limited to the poorer classes. In the tropics, the disease is commonly seen in *purdah* women who are debarred from enjoying the beneficial effects of the actinic rays of the sun. Fehling draws a relationship between the occurrence of the disease and the ovarian function and in many cases improvement followed oophorectomy. Endocrine dysfunction has also been suggested as responsible for the disease and defective suprarenal function also has been held to be a causative factor in the disease. Defective calcium metabolism is always associated with parathyroid dysfunction and this should be fully investigated in all cases. Infective causes are stated to predispose and in a few cases a severe attack of puerperal, typhoid, or scarlet fever, etc., has preceded the development of osteomalacia. Repeated pregnancies are also said to predispose. The essential pathological changes consist in the absorption of the calcium salts in the affected part of the bones leaving them fibrous and decalcified and new bone is not formed. The pelvic bones are markedly affected and are seat of deformity, though other bones such as vertebræ, ribs, etc., are also

involved. The muscles covering the bones degenerate and atrophy. The patient often complains of pain of an aching character in the pelvic region, back, chest, etc. Tenderness over the affected bones may be present, various deformities of the spine and spontaneous fractures of bones may be also met with. Fever, wasting, excessive perspiration and cardiac symptoms may also occur. Examination of urine usually reveals an excess of phosphates and calcium salts. The disease may run a course of several months and thus become chronic.

TREATMENT. Search for all septic foci in the body should be made and eradicated when detected. The general hygienic condition of the individual should be improved. An open air life and enjoyment of the beneficial effects of sunlight should be advised in these cases. The diet is most important and the selection of proper dietary is all that is required in the treatment. It should comprise foods rich in calcium, phosphorus and vitamins and these are abundantly contained in fresh milk, eggs, fish, meat and fresh vegetables particularly beans, peas, tomatoes, spinach, etc. Vitamin preparations especially containing vitamin D such as radiostoleum, ostelin, codliver oil, halibut-liver oil, etc., should be advocated. Parathyroid extract in combination with calcium therapy is of particular value in most cases. Physical therapy in the form of ultra-violet rays is beneficial in countries where natural sunlight cannot be always obtained. Aspirin, salicylates, application of heat and massage are useful for alleviation of pain and cramps. Calcium lactate has been advocated in 1 dr. doses three times daily with milk. The prolonged intake of phosphorus has given encouraging results and this may be given in solution in almond oil (1 in 1000) in daily doses of one tea-spoonful after food or phosphorous pill (1 in 100) may be given in doses of 1 or 2 gr. three times daily after food. Preparations of suprarenal gland have also given good results in some cases. If the disease progresses in spite of medicinal treatment oophorectomy is advised. Artificial abortion is justified in earlier months of pregnancy in cases of deformed pelvis with small and narrow outlet and moreover it has been found that pregnancy usually leads to a rapid development of the disease.

OXALÆMIA. It is said to result from three sources, namely, the food, intestinal fermentation and the tissues. Oxalophoric foods or foods containing considerable amount of oxalates are rhubarb, sorrel, tea, coffee and chocolate. Some hold that pure proteins and gelatine do not give rise to oxalic acid. Probably all sugar-containing foods are capable of giving rise to oxalates in the body. Intestinal fermentation, especially in the presence of tapeworms, which contain much glycogen, may also lead to the formation of oxalic acid. In the treatment of oxalæmia, foods containing oxalates are better avoided and also sugar and articles of diet which are not pure protein, such as meat, should be restricted. Fish is better tolerated in these

cases. As the liver function is generally sluggish in this condition, it should be stimulated. The alimentary canal should be freed from animal parasites, and metabolism speeded up by respiratory exercises, ultra-violet rays and oxidising remedies. Insulin appears to be the most effective drug in the treatment of oxalæmia.

PELLAGRA. See page 1029.

PLEURISY. It is not infrequently met with in the course of a large general practice, and although many cases are easily dealt with, others are liable to cause trouble and anxiety. The vast majority of cases of pleural inflammation are undoubtedly infective in origin; seldom primary, apart from tuberculosis, but generally secondary to some focal infection of the lungs (tuberculosis, pneumonia, bronchitis, abscess, gangrene, etc.). Certain cases arise (a) as a result of direct extension of disease from adjacent organs other than the lung, or from serous membranes (pericarditis and peritonitis); (b) *via* the blood stream, as a part of a general infection (septicæmia, pyæmia); (c) in the course of infections of undetermined origin (rheumatic fever, scarlet fever); (d) by the agency either of organisms or of chemical toxins in chronic disorders of metabolism (gout, diabetes, chronic nephritis); (e) by metastasis from more distant focal infections (tonsillitis, appendicitis, oral sepsis); (f) trauma (wounds, contusions, fracture of ribs); (g) from new growths of the lung; (h) as complications (bronchiectases, hydatids, etc.); (i) terminal, often in elderly subjects.

The most frequent causal agent is the tubercle bacillus. Non-tuberculous exudative pleurisy, which occurs in about 18 per cent. of all cases, is most frequently due to the pneumococcus or streptococcus. A ready clinical classification is discoverable in the nature of the effusion. Thus a dry pleurisy connotes a fibrinous exudate; a pleurisy with simple effusion is one that is sero-fibrinous and empyema is one that is definitely purulent.

TREATMENT. *Acute dry pleurisy.* The usual symptoms are pain in the chest aggravated by coughing or attempts at deep breathing with slight or moderate fever. The characteristic physical sign is a fine friction sound, audible over the area affected.

General management. Complete rest in bed, plenty of fresh air in accordance with the state of the patient; a dose of calomel is administered at the beginning followed by salts in the morning. In the earliest stage, small doses of tincture of aconite or veratrum viride, 2 min., every quarter of an hour during one hour, afterwards repeating the dose hourly, until the skin begins to act freely and the temperature abates. Such remedies should be discontinued as soon as the circulation becomes relieved.

Pain. (a) *Local applications.* Mild cases are relieved by thermogen wool used dry or rendered more potent in action by sprinkling with warm salt and water, by the employment of the official cataplas-

ma kaolin. Failing this, turpentine or belladonna stupes, or hot linseed meal poultices find some advocates. Strapping the chest, which in former days was normal routine except for cases in which pain is intense, is less to be recommended since it tends to embarrass the sound side, prevents effective auscultation, and during removal is apt to cause pain and disturbance to the patient. Dry cupping has again come into favour. For very intense pain, a good procedure is to introduce into the pleural sac a small quantity, say 200 c.cm. of filtered air which, by separating the inflamed pleural layers, acts as a cushion and gives instant and complete relief. (b) *Drugs*. At the beginning, for slight pain, Dover's powder 10 gr. is excellent; aspirin 10 gr. with or without pyramidon (5 gr.) may be given. Internally an alkaline diaphoretic and diuretic is of use, e.g., potassium citrate 20 gr., ammonium acetate solution 2 dr., syrup of lemon 1 dr.; camphor water $\frac{1}{2}$ oz. six hourly. If the pain increases and the patient becomes restless and irritable, it may be necessary to have recourse to veramon 6 gr., by mouth, repeated if necessary or to a hypodermic injection of morphine $\frac{1}{6}$ to $\frac{1}{4}$ gr.

Insomnia. If no cause is obvious, in mild cases 15 gr. each of potassium bromide and chloral hydrate will suffice; in moderate cases, allonal one to two tablets or medinal 5 to 10 gr., in the worst cases omnopon $\frac{1}{3}$ gr. orally or hypodermically.

Cough. This is usually dry, persistent and ineffective and requires the exhibition of a suitable tincture, such as glycerine 20 min., syrup of lemon 15 min., water to 1 dr., to which may be added, if necessary, heroin hydrochloride $\frac{1}{20}$ gr. or morphine hydrochloride solution 3 min. In dry chronic pleurisy resolution may be hastened by counter irritation in the form of mustard plaster or blisters, or by painting the chest wall with equal parts of liniment or tincture of iodine. Internally a mixture may be prescribed containing the following: Potassium iodide 10 gr., sodium bicarbonate 20 gr., sodium salicylate 10 gr., ammonium carbonate 3 gr., chloroform water up to $\frac{1}{2}$ oz., thrice daily.

In acute pleurisy with simple sero-fibrinous effusion, fever, cough and pain may subside after a week or so, and a slight serous exudate becomes absorbed. The process may be quickened by painting the chest with iodine, or by dry cupping. If the exudate does not exceed moderate limits, treatment is similar to that for acute dry pleurisy. A light diet with limitation of total fluids is advisable, the bowels being kept open with concentrated salines. Effusion extending above the fourth rib anteriorly, if left alone, naturally tends to take longer to absorb than those of less amount, disappearance of the fluid being accompanied by crackling or creaking friction sounds. For many months, at the base of the affected lung resonance is impaired, and breath sounds are but feebly audible. If after three weeks the fluid level stands at the same height, or is increasing, particularly above the fourth rib in front or if displacement of organs causes circulatory or respiratory

embarrassment, after determination of the nature of the fluid by an exploratory puncture, syphonage or aspiration should be undertaken, unless the fluid is hæmorrhagic. Tapping too low on the left side may damage the spleen, causing bad hæmorrhage. Needling a solid lung may cause catastrophe. In exploring the chest a local anæsthetic should always be used. The anæsthetic may be novocaine, percaine, phenolaine, or any other compound. The method of withdrawing quantities of fluid with a 20 c.cm. syringe should not be indulged in; some air is bound to enter each time the syringe is removed, this air may be troublesome or even a danger later.

Usually after the withdrawal of a small quantity of fluid or auto-serotherapy, absorption begins to take place and the patient may be left alone, but in some cases a second tapping may be necessary. There are several points in favour of leaving the fluid, firstly, antibodies may be present in the fluid, and secondly the mechanical effect. If a lung has been forcibly collapsed with a pressure of fluid, it does not expand freely at once if all the fluid is drawn off. There are those who suggest that the fluid should be drawn out and replaced by air on the assumption, firstly, that the fluid is toxic, and, secondly, that the lung should be kept collapsed. If the pleural exudate were secondary to pulmonary disease this would be justified on the analogy of the artificial pneumothorax treatment; but in most cases the lung does not appear to be diseased at the time of the effusion, pulmonary disease not appearing in most cases till some years after the effusion, during which time the patient has usually had perfect health. The assumption that air replacement is advisable in all cases would seem to be based on a false analogy. Hæmorrhagic effusions are met with in tuberculosis, influenza, neoplasm and other infected conditions of the pleura, and probably the frequency of incidence is in the reverse order to which they are mentioned. The pleura has strong antibacterial powers for dealing with infection; it is on this account that one so frequently finds that fluids which contain organisms become absorbed without going on to empyema.

PNEUMONIA. It is a disease which affects persons of all ages and stations of life. While the diagnosis as a rule affords no difficulty the prognosis and treatment call for the greatest skill and judgment. In the primary form of the disease, the infection is a self-limited one. Besides natural variation in the virulence of the infecting organism the general resistance of the patient plays an important part in the progress of the disease.

The two main types of pneumonia are: (1) Croupous or lobar pneumonia, and (2) lobular or broncho-pneumonia. Lobar pneumonia may be defined as an acute infectious disease caused by the pneumococcus of Frankel, and locally resulting in an inflammatory consolidation of a large area of the lung. The disease is now looked upon as being

primarily a form of septicaemia, the involvement of the lung being merely a local and predominating manifestation of the infection. Recent serological investigations have shown that there are four clearly defined types of infection, of which two are common, and the type 3, although the most virulent is the rarest. In type 4 the disease is said to run rather a mild course. In a typical case of pneumonia the diagnosis is not difficult, but in children, especially in apical pneumonia, the meningeal symptoms may mask the real trouble. The rapidity and type of respiration is the best guide.

Lobular, or broncho-pneumonia. The condition may be defined as an inflammation of the capillary or terminal bronchioles and the alveoli which constitute the corresponding pulmonary lobules. There are two forms of the disease, primary and secondary. In the former the pneumococcus is usually found, but in the latter the streptococcus, micrococcus catarrhalis, and Pfeiffer's bacillus are often predominant, a mixed infection indeed is usual. Broncho-pneumonia is not a self-limiting disease like lobar pneumonia and after a variable period the temperature falls by lysis.

TREATMENT. I. General. Fresh air, a minimum of disturbance and adequate nursing are essential. The propped up posture usually gives greater comfort. Gentle tepid sponging 2 to 4 times a day or as required. The diet should contain plenty of fluids; milk, citrated and diluted with water, imperial drink, barley water, horlick's malted milk, weak tea, etc. are given. The total milk in the day should not exceed two pints. Glucose or lactose may be added to each feed with advantage. Oral hygiene is important. The mouth should be cleaned with listerine or weak sodium bicarbonate solution. The bowels are kept regular with enema.

II. Specific therapy (see serum therapy, page 803). Fresh interest has recently been aroused in this subject by the use of Felton's concentrated anti-pneumococcal serum. Serum is of value only in types I and II cases which are usually responsible for from half to two-thirds or more of the total cases of primary pneumonia. It should be given in all severe cases (I and II) seen early in the diseases especially during the first 3 days. For therapeutic use the serum is supplied in phials containing 10,000 to 20,000 protein units each of types I and II in a volume of 5 or 10 c.cm. respectively. It is essential that the serum should be administered intravenously and in most cases a morning and an evening dose suffice. Dose 20,000 to 40,000 units. This serum is difficult to prepare and very expensive and uncertain in its effect. The dose required costs £10 to 20 or about Rs. 200.

III. Symptomatic treatment. (a) Pain. Morphine $1/6$ to $1/4$ gr. combined with atropine $1/100$ gr. is given during the first three days of illness to relieve pain. It should be avoided in the presence of marked cyanosis or generalised bronchitis with abundant secretion.

Other measures for the relief of pain consist of the application of anti-phlogistine or cataplasma of kaolin. (b) For cough a sedative linctus along with a hot drink and steam inhalation is helpful. In early stages a simple alkaline diaphoretic mixture—potassium acetate 20 gr., potassium citrate 30 gr., ammonium acetate 2 dr., spt. of nitrous ether 15 min. and water 1 oz. is helpful; it loosens the sputum and promotes diuresis and elimination of toxins. In later stages and when there is much bronchitis a stimulant expectorant mixture consisting of sodium bicarbonate 10 gr., ammonium carbonate 5 gr., tincture of scilla 10 min., chloroform water 1 oz. is given. (c) To produce sleep give in the early stage, omnopon 1 gr. or Dover's powder 10 gr., later chloramide and potassium bromide 20 to 30 gr. of each., paraldehyde 1 to 2 dr., medinal 6 gr. (d) Stimulants. Digitalis 10 to 15 min. of the tincture 6 hourly. The early administration of digitalis is a safeguard to the heart. The action of strychnine on the respiratory and vasomotor centres makes it a valuable drug in the stage of falling blood pressure; give subcutaneously in doses of 1/60 gr. 6 hourly alone or combined with atropine 1/100 gr. Adrenalin 0.2 c.cm., pituitrin 0.3 c.cm. may be given intramuscularly when the pulse begins to flag. Camphor in oil or cardiazol are very valuable cardiac stimulants. Dose 1 c.cm. every 4 to 6 hours. Glucose acts as a stimulant to the exhausted heart muscle in acute failure and may be given intravenously—50 c.cm. of a 20 per cent. solution with 10 units of insulin subcutaneously and repeated in 12 hours if necessary. Alcohol is given when indicated and not as a routine. Oxygen is administered with a catheter at the earliest evidence of cyanosis. Tonics are indicated during convalescence, e.g., perchloride of iron sol. 10 min., strychnine hydrochloride sol. 3 min., glycerine 30 min. and water to 1 oz. Cod liver oil may also be given.

POISONING. *General directions.* (1) In all cases where the poison has been taken by mouth, immediately empty out the stomach either by a stomach tube, or emetics. The stomach tube is contraindicated in poisoning with corrosives, strong alkalies and acids; it should be used cautiously in irritant poisoning. Emetics should only be used when no means of washing out the stomach are at hand; where poison has been taken immediately after or along with full meals, emetics should first be used followed by a stomach tube. Emetics are also contraindicated in corrosives, strong acids and alkalies; when much diluted they do not act promptly. (2) Do not wait for symptoms to appear even in suspected cases; act promptly and wash out the stomach at once. (3) Always keep the contents of the stomach and first washings (with plain water) for chemical examination. (4) Stomach washings should be thorough and repeated at intervals when symptoms reappear.

THE FOLLOWING INSTRUMENTS AND ANTIDOTES SHOULD ALWAYS BE KEPT READY FOR TREATMENT:—*Instruments.* Stomach tube (this should be in-

spected frequently as rubber is liable to perish and become unserviceable), mouth gag, rubber catheters, hypodermic syringe, tourniquet, scalpels, rectal tube and saline apparatus.

Emetics. Apomorphine hydrochloride 1/10 gr. tablets, zinc sulphate 30 gr. in 4 oz. warm water; copper sulphate 10 gr. in 4 oz. warm water; mustard $\frac{1}{2}$ oz. in 8 oz. of tepid water; ipecacuanha wine 6 dr.

Stimulants. Strychnine hydrochloride 1/30 gr. tablets; digitalin 1/100 gr. tablets; ether in glass ampoules; adrenalin, brandy; coffee; ammonium carbonate, sal volatile.

Opiates. Morphine hydrochloride 1/3 gr. tablets; tinct. of opium 30 min. or more.

Antidotes. Atropine sulphate 1/60 gr. tablets; pilocarpine nitrate $\frac{1}{2}$ gr. tablets; pituitrin 1 c.cm. ampoules; amyl nitrite capsules; gold chloride one per cent. solution; potassium permanganate crystals; tea; tannic acid; carbonates of sodium and magnesium; olive oil; castor oil; lime water; sulphates of sodium and magnesium; strong ammonia solution; ferrous sulphate; tincture of perchloride of iron; vinegar, citric acid; starch; sodium bicarbonate, dilute sulphuric acid and tinct. of iodine; potassium bromide; chloroform; antivenine; oxygen.

Warmth. By hot bottles or friction to the extremities.

Demulcents. Milk, white of egg, barley water, olive oil (avoid in phosphorus and cantharides cases), linseed, tea.

Saline injections. Normal saline, either by the rectum or sterilised and given intravenously or subcutaneously.

ACIDS. *Hydrochloric, nitric and sulphuric.* Do not use the stomach tube or emetics, but give alkalis, such as calcined magnesia, lime water, if not available give chalk, whiting, sodium carbonate, or potassium carbonate dissolved in plenty of water; magnesium carbonate may also be given dissolved in water or soap and water in large draughts followed by demulcents, opiates and stimulants, if required. To relieve thirst give pieces of ice or ice cream. Rectal feeding to maintain nutrition. Tracheotomy may be required to relieve dyspnoea.

Carbolic acid. Use a soft stomach tube gently and carefully and wash out successively with magnesium sulphate or sodium sulphate $\frac{1}{2}$ oz. in a pint of warm water, until there is no smell of carbolic acid in the washing. Leave some of the solution in the stomach. Follow this up by demulcents, stimulants, warmth and artificial respiration. Intravenous or rectal saline, if necessary.

Oxalic Acid. Do not use the stomach tube or emetics, give chalk, whiting or lime with plenty of water. Give milk freely and follow with a full dose of castor oil and stimulants.

Hydrocyanic acid or cyanides. Prompt action essential. Place the patient in the fresh air. Give adrenalin 4 dr. (1 in 1,000) by mouth, empty stomach and wash out with pot. permanganate solution. 15 gr. of sulphate of iron with 20 min. of tinct. ferri perchlor. in a little water adding 2 dr. of magnesium carbonate. Mix and administer and repeat

if necessary. Artificial respiration, cold douche (from a height) to head and spine. Ammonia inhalations. Strychnine hydrochloride 1/15 gr. and ether over the heart area; atropine sulphate 1/60 gr. hypodermically. If the body surface is cold, vigorous friction and hot applications. Intravenous injection of glucose or sodium thiosulphate (10 per cent. sol.) 5 c.cm.

ALKALIES. *Caustic potash, caustic soda, ammonia.* Do not use the stomach tube or emetics, but give weak acids, such as vinegar diluted in water or citric acid, tartaric acid, lime juice, $\frac{1}{2}$ dr. to one pint of water. Repeat. Followed by demulcents, opiates and stimulants.

INORGANIC POISONS. *Antimony.* Wash out the stomach, give strong tea, tannic acid 30 gr. in warm water, repeating as often as vomiting occurs. Demulcents, stimulants, opiates, warmth. Pituitary extract and saline injection if needed.

Arsenic. Wash out the stomach thoroughly. Give freshly prepared ferric oxide. (Mix one and a half ounces of tinct. ferri-perchlor. in a wine-glass of water with a solution of sodium carbonate $\frac{1}{2}$ oz. in half a tumblerful of water, strain the precipitate and administer the precipitate suspended in a glass of water). Repeat, if necessary. Demulcents. Stimulants. Opiates. Ice to suck. Warmth to extremities. Saline injections or saline per rectum. Sodium thiosulphate 5 c.cm. (10 per cent. sol.) intravenously.

Copper salts. Give large quantities of milk and eggs. Then wash out the stomach. Demulcents, opiates, and stimulants.

Iodine. Wash out the stomach with a soft tube. Sodium bicarbonate 2 dr. in half a tumbler of water. Starch, bread, rice-water, milk and flour, morphine. Stimulants.

Lead salts. Wash out the stomach. Give magnesium or sodium sulphate $\frac{1}{2}$ oz. in 8 oz. of water or dilute sulphuric acid 30 min. in 8 oz. of water. Demulcents. Morphia.

Mercury and its salts. Give large quantities of milk and eggs before attempting to wash out the stomach. Demulcents. Tincture of opium and stimulants. Repeat stomach washing and continue it. Rectal irrigation with saline, mouth wash with astringents. Alkaline normal saline intravenously, if necessary. Sodium thiosulphate 5 c.cm. (10 per cent. sol.) intravenously once every day when acute symptoms subside.

Phosphorus (red paste matches). Wash out the stomach thoroughly with potassium permanganate solution. (1 gr. to 1 oz.) and leave about 10 oz. in the stomach or give copper sulphate 2 to 3 gr. in 4 oz. of water every five minutes until vomiting is induced; then every 15 to 30 minutes and then wash out the stomach with potassium permanganate solution or weak hydrogen peroxide. Old French Turpentine 40 min. emulsified with mucilage and water every 15 minutes for the first hour, then three times daily. Magnesium sulphate $\frac{1}{2}$ oz. as a purge. Demulcents. Normal saline with sodium bi-

carbonate intravenously to combat shock and diminished alkalinity of blood. Avoid oils and fats.

Silver salts. One ounce common salt in 8 oz. of water. Then wash out and follow with white of egg and milk.

Zinc salts. Large quantities of milk and white of egg, large quantities of sodium or potassium carbonate dissolved in warm water. Tannic acid, strong tea, demulcents and opiates, if necessary.

ORGANIC POISONS. *Aconite.* Wash out stomach with dilute potassium permanganate solution. Digitalin 1/100 gr. or better 1/50 gr. Atropine sulphate and also strychnine. Maintain recumbent position. Stimulants. Artificial respiration. Friction. Warmth. Brandy diluted with water per rectum.

Alcohol. Wash out stomach. Ammonium carbonate 30 gr. in 5 oz. of water. Strong coffee, strychnine hydrochloride 1/60 gr. Keep the patient roused with cold douches. Digitalis. Warmth. Artificial respiration. If required, oxygen inhalation.

Antipyrin group (antipyrin, antifebrin, phenacetin) Wash out stomach. Recumbent position. Warmth. Stimulants. Digitalis. Strychnine hydrochloride. Artificial respiration. If necessary, oxygen inhalation.

Belladonna, atropine, datura, hyoscine. Wash out stomach with dilute potassium permanganate solution. Pilocarpine 1/3 gr., repeated every two hours until skin becomes moist. Stimulants, tea, coffee, tannin. Warmth. Artificial respiration. Catheterise, if urine retained. If delirium is great, give sedatives and ice bag to head.

Cannabis indica. Wash out stomach with dilute potassium permanganate solution. Purgatives. Brandy. Tannin.

Cantharides. Apomorphine 1/10 gr. and strychnine hydrochloride 1/60 gr.; give alkalies freely. White of eggs. Barley water, gruel. Stimulants. Morphine. Avoid oils and stomach tube.

Chloral. Wash out stomach. Strychnine hydrochloride 1/60 gr. Warmth and friction are essential. Hot coffee. Stimulants. Artificial respiration. Oxygen.

Chloroform. (By inhalation). Pull out the tongue. Swab any mucus from the back of the throat, place the head lower than the body. Artificial respiration. Atropine sulphate. Strychnine 1/60 gr. with digitalin and ether hypodermically. Brandy and coffee per rectum. Massage the heart per abdomen. Intracardiac injection of adrenalin solution. Oxygen inhalation. Wash out stomach well, stimulants for the heart and respiration as above.

Cocaine. Wash out the stomach with dilute potassium permanganate solution. Strychnine and digitalin hypodermically, adrenalin intramuscularly, ammonia or amyl nitrite to inhale. Recumbent position. Artificial respiration. Strong coffee. Bromides or morphia, if convulsions.

Croton oil, colchicum and violent purgatives. Wash out stomach with milk or olive oil. Demulcents. Stimulants. Opiates.

Digitalis. Wash out stomach with dilute potassium permanganate solution, give strong tea or coffee. Tannic acid 10 gr. in 2 oz. of water by mouth repeated frequently. Recumbent position. Warmth Stimulants. Atropine injection for slowness of heart.

Fungi. Wash out stomach with dilute potassium permanganate solution. Atropine 1/50 gr. Stimulants. Warmth. Castor oil. Opiates.

Food-poisoning. As for fungi, but avoid atropine.

Kerosine oil, paraffin, petroleum. Wash out stomach. Strychnine. Warmth. Hot coffee per rectum. Demulcent. Castor oil. Artificial respiration.

Oleander. See digitalis, page 246.

Opium. Wash out stomach with tepid water tinted with potassium permanganate ($\frac{1}{2}$ gr. to 1 oz.) until the pink colour is retained in the return washings. Leave about 10 oz. in the stomach. Every if morphia is taken hypodermically, wash out the stomach with permanganate solution. Repeat washing after half an hour. If symptoms reappear, wash out again. Atropine sulphate 1/30 gr. repeated, if necessary. Strychnine and ether hypodermically. Keep the patient roused with cold douche, or walking to and fro between two assistants (in mild cases only). Forced walking contraindicated in collapsed or comatose cases. Ammonia or smelling salts to nostrils. Artificial respiration. Hot coffee by mouth, or per rectum. Warmth. Oxygen.

Tobacco. Wash out stomach. Recumbent position. Strychnine. Strong tea. Stimulants. Warmth. Artificial respiration.

Strychnine, nux vomica. Administer ether or chloroform until introduction of stomach tube is possible. Wash out stomach with tannic acid or potassium permanganate solution. Leave a mixture of chloral hydrate 30 gr. and potassium bromide 1 dr. in the stomach or give apomorphine hydrochlor 1/10 gr. for emesis. Chloroform inhalation or chloral hydrate per rectum to control spasms, if necessary. Absolute quiet in a dark room essential. Warmth. Artificial respiration. Oxygen.

Turpentine. Wash out stomach. Magnesium sulphate 1 oz. in water. Morphine. Demulcent drinks.

Sulphonal, trional, veronal, medinal, luminal. Wash out stomach, leaving one pint of hot coffee with an oz. of castor oil (or give emetic). Stimulants. Warmth. Recumbent position. Artificial respiration. Subcutaneous saline. Catheter, if necessary.

Gas poisoning (carbon monoxide, carbon dioxide, marsh gas, coal gas, sewer-gas). Fresh air, inhalation of oxygen, ammonia to nostrils. Stimulants. Warmth. Strychnine. Digitalin. Artificial respiration. In carbon monoxide poisoning attempts should be made to cause the patient to breathe in the expired air of the medical attendant through a tube made of stiff paper. Venesection and transfusion of blood may be tried.

POLIOMYELITIS, ACUTE. (Infantile paralysis). It is an acute specific fever characterised by lesions in the grey matter of the anterior horns of the spinal cord. Von Heine (1840) discovered that the lesion was localised in the spinal grey matter. Landsteiner and Papper (1909) indicated that the disease was due to a filterable virus and transmitted the disease to monkeys. Infection is usually acquired by the nasopharyngeal route and the virus is transmitted from patients as well as by carriers, milk and fomites. The histological features of the cord lesions are perivascular infiltration of the grey and white matter with degeneration of the ganglion cells of the anterior horn. A single attack gives permanent immunity to the individual. The incubation period is 3 to 10 days. The onset is usually sudden with headache, malaise and gastro-intestinal disturbance; the temperature rises high. This prodromal stage is usually very short. Muscular paralysis is noted about the second or third day and usually does not progress from the start, but in some cases spreads rapidly. Various types of the disease are described, of which the commonest is the spinal variety. Leg muscles are commonly affected; in some cases one arm and the other leg are affected, but all four limbs may be paralysed; reflexes are lost; a maculo-papular eruption may be seen on the affected limb. Besides this spinal type Wickman described certain other varieties, *viz.*, abortive spreading (ascending or descending), meningeal, cerebellar, cerebral, and mixed types. The cerebrospinal fluid is clear and under pressure and there is an excess of cells present; the protein is increased; the sugar and chlorides are normal, and no organisms are found. The blood examination shows leucocytosis.

TREATMENT. Absolute rest in bed is essential. Paralysed limbs should be wrapped up in cotton wool and well supported. If the serum of a convalescent patient is available it should be given early. About 30 c.cm. of blood are taken from the convalescent, the serum is separated and warmed to body temperature. Lumbar puncture is then performed on the patient, 10 to 15 c.cm. of the spinal fluid are removed and the serum is injected intrathecally. Attempts are being made to prepare a protective vaccine on the lines of the anti-rabic treatment. Hexamine is often given with alkalis by mouth, but its value is doubtful; aspirin may be given for pain and sedatives for restlessness. The muscles should not be massaged during the active stage of the disease. After a month or so gentle massage and electrical treatment may be applied.

Prophylaxis. The patient should be isolated for 3 weeks after the temperature is normal. Contacts should gargle twice a day with potassium permanganate solution (1 in 5,000).

PREGNANCY TESTS. *Aschheim-Zondek* ^{4b}*Pregnancy test.* The test depends upon the fact that the urine of a pregnant

woman contains a substance which induces the formation of hæmorrhagic follicles in the ovary of the sexually immature female mouse.

Female mice, three to four weeks old and weighing about 6 to 10 gr. are used in the experiment. The age factor is important as the ovarian cycle in the mouse commences at about the sixth week of life. Five animals are used in each test. The urine for injection should be fresh and a morning specimen. Aschheim and Zondek recommended that each of the five mice should receive a different dose; thus the first would receive six doses of 0.5 c.cm.; the second six doses of 0.4 c.cm. and so on. It has been found that the mouse receiving the largest dose gives a weaker response than others receiving smaller doses. The injections are completed in 48 hours as follows: first day in the morning and evening; second day in the morning, mid-day and evening; third day only in the morning. *Condition of the ovary.* On the morning of the 5th day a naked eye examination of the genital apparatus of the animals is undertaken. Three types of reaction are observed in the ovary. These are called by Aschheim and Zondek as the anterior pituitary reaction (Hypophysen Vorderlappen Reaktion). I. This consists in the formation of large mature follicles in the ovary. II. This consists in the formation of hæmorrhagic follicles. III. This consists in the formation of *corpora lutea*. Reactions II and III separately or together indicate a positive result whereas reaction I alone implies a negative one. *Condition of the uterus.* In reaction I the uterus appears to be considerably enlarged in size and distended with fluid. The ovary is sometimes found to be full of corpora lutea with the formation of hæmorrhagic follicles and the uterus closely resembles one of an untreated animal. *Condition of the vagina.* The vagina of the animal in reaction I is found to be open. A smear is characteristic of œstrus.

Apart from pregnancy, the reaction I is obtained in certain other conditions such as after the menopause (25 per cent. of cases), castration and in cases of genital carcinoma.

Hofman's hormonal pregnancy reaction. The test differs from the original Aschheim Zondek test in that the blood serum is used instead of urine. Sometimes, a hormonal blockage in the kidney results, which gives negative pregnancy reaction, and so Hofmann tried the test with blood serum. The blood serum can be withdrawn any time during the test, whereas it is sometimes difficult to procure the morning specimen of urine. Rabbits were used as test animals because the pregnancy test can be completed in less than four days with rabbits, whose ovulation mechanism differs from that of mice. In order to eliminate certain sources of error involved in the rabbit test, such as pseudo-œstrus, infantilism, dermoid cysts, an exploratory laparotomy is performed to inspect the ovaries of the animals, immediately before the test. *The technique of the test* is as follows; 25 c.cm. of blood, which may be withdrawn from the patient at any time, is centrifugalised and the serum shaken with ether. A female rabbit weighing not less than 2,300 gm. is

laparotomized and the ovaries are inspected. Then approximately 13 c.cm. of serum is slowly injected into the marginal vein of the ear. If the animal does not tolerate it well, the injection should be interrupted and continued about an hour later. Twenty-four hours later, the ovaries are inspected and the presence of blood clots indicates pregnancy in the woman from whom the blood specimen was taken.

Biochemical test. This test is based on the facts that the prehypophyseal hormone increases the cholesterol content of the blood and that the urine of a pregnant woman contains the prehypophyseal hormone. The injection of urine of pregnant women into guinea-pigs of either sex produces within the first 24 hours an increase of cholesterol in the blood amounting to from 30 to 50 per cent. The reaction is positive at various stages of pregnancy. In a control series of experiments it was found that urine of non-pregnant women did not produce this increase of cholesterol in the blood. *The technique:* 10 c.cm. of urine obtained from the fasting patient by catheterization is mixed with 25 c.cm. of sulphuric ether. After the mixture has been shaken and decanted, 10 c.cm. of it are injected into a guinea-pig. After 24 hours, blood is withdrawn from the heart of the animal and the cholesterol content of the blood is determined. This test of hormone hypercholesterolaemia is considered positive if the blood cholesterol of the guinea-pig is increased to 25 per cent. The test has several advantages over the Aschheim-Zondek reaction. The test animal is easier to procure as it may be male or female, sexually mature or immature and of any age or weight. The technique is simple and the test can be performed in 24 hours.

Chemical test. (a) To one c. cm. of urine add one drop of a 0.5 per cent. solution of hydrogen peroxide followed by 5 drops of a 1 per cent. aqueous solution of phenyl hydrazine hydrochloride, 5 drops of a 5 per cent. aqueous solution of methyl cyanide and 5 drops of concentrated HCl. Place the mixture in a water bath for 25 minutes. A russet colour and flocculent precipitate denote a positive reaction whilst a negative reaction is indicated by a straw colour and a powdery precipitate or the complete absence of a precipitate. (b) A second method said to be more sensitive is as follows. To 1 c.cm. of urine add 1 drop of a 0.5 per cent. solution of hydrogen peroxide and allow to stand for 3 minutes. Then add 5 drops of 1 per cent. solution of phenyl hydrazine hydrochloride, followed by 5 drops of a 5 per cent. aqueous solution of potassium ferricyanide. Allow the mixture to stand at room temperature for ten minutes; next, place it in a boiling water bath for 15 minutes. Add 1 drop of concentrated HCl followed by an excess of sodium hydroxide; then titrate with dilute hydrochloric acid until the colour changes from orange through green to blue. Much less diluted HCl was required to produce the final colour in pregnancy urine than in the urine of women who were not pregnant. The reagents must be fresh.

PRURITUS. It is a subjective sensation of itching. The causes are manifold. (1) Hysterical pruritus is seen in young girls and also in older women about the menopause. Other symptoms of hysteria such as anaesthesia of the soft palate and of the cornea are also evident. (2) 'Nervodermite' is seen in the middle-aged women, and the parts affected are nape of the neck, labia, perineum and thighs. (3) In psychological cases though pruritus has long ceased, the patient is still under the impression that he or she is suffering from it. (4) Senile pruritus. (5) Cases of dermatographism. (6) Toxic pruritus of diabetes, gout, hepatic affections, Grave's disease, visceral carcinoma, malaria, nephritis, focal sepsis and also pruritus due to drugs and food is known. (7) A few external causes are: (a) Parasitic disease, e.g., pediculosis, scabies, ringworm. (b) Pruritus ani and vulvæ may be due to worms, portal congestion due to hepatic disease or local obstruction from tumours in the pelvis and from pressure of the uterus in late pregnancy, local fissures or secondary eczema.

DIAGNOSIS. (1) History. (2) Local examination of the part. (3) Regions of the body affected. (4) Laboratory examination.

TREATMENT. *General.* Investigate the cause and treat accordingly. Nerve sedatives are helpful in the nervous group of cases. Women nearing the menopause are best treated by radium which accelerates the cessation of menstruation. In toxic cases, remove the cause first. Investigate if there is intestinal stasis and if so treat by the combined fast and purge method (preferably with the salines). Eradicate septic foci in the body. If an allergic state is suspected, do a Walker's food test and correct dietetic errors. If no definite cause is ascertained try symptomatic treatment with soothing lotions and other general sedatives.

Local. Application of hot compresses followed by dusting inert powders. Soothing lotions, e.g., carbolic acid (1 to 2 per cent.), dilute hydrocyanic acid used as lotion or ointment, 1 to 3 per cent., camphor in oil, 1 to 10 per cent. menthol as ointment, 10 per cent. Bayer's cycloform ointment; 1 to 3 per cent. ichthyol may be added to the above lotions or ointment.

A useful prescription is, carbolic acid (1 in 80) 1 oz., liq. carb. detergens (1 to 6 per cent.) 15 min. Spa treatment, if available, is very beneficial in some cases. Regulation of habits should form a part of the treatment. Calcium and parathyroid are very useful in many cases and particularly in those of dermatographism. Adrenalin is also useful in such cases for temporary alleviation.

PYORRHOEA ALVEOLARIS. It is a disease characterised by a progressive inflammation and ulceration commencing at the gum margin and invading the periodontal membrane. There are various methods of treating pyorrhoea which should be used in combination with full co-operation of the patient. The methods usually employed are:

(1) Scaling of the teeth to remove all tartar especially that adherent to the roots. (2) Massage of the gums with glycerine and tannic acid is useful. The procedure is to wrap a piece of muslin round the finger and dip it in the above. The gums should be vigorously rubbed both transversely and vertically and on both surfaces. This should be done for a few minutes twice a day for about 3 weeks at least after the scaling. It may then be replaced by a solution of salt water, a teaspoonful of salt to a tumbler of water. (3) Mouth washes. Their main purpose is to flush out the mouth and to remove debris. The idea of killing bacteria with strong antiseptics is fallacious. If antiseptics are used they must be very well diluted. The following gargles are usually used; saline, potassium permanganate, hydrogen peroxide, chinosol, listerine, alum and potassium chlorate.

The patient should brush his teeth at least twice a day (morning and night) and rinse the mouth thoroughly after each meal.

GENERAL TREATMENT. (a) *Regulation of the bowels*, (b) *tonics*, (c) *sufficient fruits in diet*.

VACCINE THERAPY. It has little if any value in the treatment of pyorrhœa.

PYREXIA. (See page 202). If one cannot remove the cause of the fever, that is to say, deal with the cause radically, it is best only to try to keep the temperature within bounds. To attempt to force down a temperature too zealously may do more harm than good. The principles of treatment in any case in which fever is a prominent symptom are: (1) Removal of the cause if possible. (2) Maintenance of the patient's strength until the disease has run its course. This is mainly a question of general management and diet. The diet should be light and nourishing. In this country milk is usually the chief article of a liquid diet. Two or three pints a day should be the maximum allowance, given in 6 to 8 oz. feeds at a time. The milk may be flavoured in various ways with tea, coffee, cocoa, etc. to avoid monotony. The milk may be supplemented by broths, fruit juices and lemon drinks sweetened with sugar. Water should be given freely. If the patient is able to take solids, the range of choice in diet is much widened. Foods rich in starch and sugar are the best. These include cereal foods (bread, rice, cornflour, arrowroot, etc.) and fruits. Alcohol may be used, but most febrile patients do quite well without it. The common practice in this country is to use brandy. (3) Measures to modify the fever. (a) By lessening heat production. We have no means of materially lessening the production of heat. (b) By acting on the heat-regulating centres. The antipyretics of the coal tar group (antipyrin, aspirin, pyramidon, etc.) act in this way. But their routine use is condemned. (b) By increasing heat loss. This is the only legitimate way of reducing the temperature in cases of fever. This may be effected more actively either (i) by promoting perspiration and so

increasing the loss of heat by evaporation or (ii) by the direct removal of heat from the body by hydrotherapy.

The production of sweating by diaphoretic drugs has long been one of the main objects of treatment of acute fever. The following is often used (potassium acetate 15 gr., liq. ammonium acetate 2 dr., spirit of nitrous ether 15 min., lemon syrup 1 dr., camphor water up to 1 oz.). The direct removal of heat by hydrotherapy is very effective. This consists of an ice bag on the head, sponging, bath, wet pack and iced rectal saline.

TEMPERATURE NORMAL. Mouth 96.7° to 99°F., Rectum 97.2° to 99.5°F. (most reliable), Axilla and groin 0.4°F. below the rectal.; temperature in a stream of urine 0.3° to 0.5°F. below rectal. In the tropics temperature is about 1°F. higher than in a temperate climate. The temperature is maximum in the evening (between 5 p.m. to 8 p.m.) and minimum in the early hours of the morning. The daily temperature range in health is 1° to 1.5°F.

A temperature of 100°F. is regarded as slight fever, 102°F. as moderate fever, 104°F. as high fever and 105°F. or upwards as hyperpyrexia.

TYPES OF PYREXIA. (I) *Continued or continuous fever*. Diurnal variation often does not exceed the normal diurnal variation; seen in typhoid fever, diphtheria, influenza, rheumatic fever, pneumonia, glandular fever, plague, undulant fever, yellow fever, cerebrospinal fever, trench fever, relapsing fever, rocky mountain fever, and kala-azar. (II) *Remittent pyrexia*. Here the temperature never attains normal though the diurnal variation is greater than the average diurnal variation. (III) *Intermittent pyrexia*. Temperature sometimes is normal and sometimes raised a degree or two, generally towards the evening. Types II and III seen in malaria, latent tuberculosis, visceral syphilis, subacute septic conditions, enteric group of fevers, pernicious anæmia and trypanosomiasis.

QUINSY. See page 1473.

RABIES. See page 1004.

RADIOTHERAPY. See page 136.

RASHES DUE TO DRUGS. Erythematous rashes, generally localised masclar eruptions confined to the arms, face and trunk, sometimes widespread and resembling measles and scarlatina.

(a) Animal sera—5 to 10 days after injection; the rash appears with malaise, fever and joint pain.

*(b) The coal tar products—antipyrin, phenacetin. The synthetic salicylates produce macular rashes extensively distributed over the trunk and extremities.

(c) Quinine, copaiba, cubebs, belladonna, opium and its derivatives—blotchy macular eruption on trunk and extremities.

(d) Allonal, luminal, veronal, etc. Arsenic, bromides, iodides, phenolphthalein, chloral and turpentine, produce macular, papular or diffuse scarlatiniform rashes involving the whole body.

Acute exfoliative dermatitis—arsenic, ar-phenamine, bismuth.

Urticarial eruptions—animal sera, arsenic, iodides, bromides, quinine, phenacetin, phenolphthalein (these may also produce eruptions of erythema multiforme type).

Vesicular eruptions—arsenic, bromides, iodides, quinine, antipyrine, and chloral.

Bullous eruptions—iodides, bromides, chloral, antipyrine, phenolphthalein, synthetic salicylates.

Pustular eruptions—iodides, bromides, chloral, antipyrine, arsenic, arsphenamin, synthetic salicylates, turpentine.

Acneform eruptions—iodides, bromides, chloral, turpentine.

Vegetating granulomatous conditions—arsenic, iodides, and bromides.

Ulcerative and gangrenous—iodides, bromides, arsenic, chloral and quinine.

Hæmorrhagic (patches of ecchymosis or purpuric spots)—animal sera, arsenic, arsphenamine, antipyrine, bromides, copaiba, ergot, iodide, quinine, synthetic salicylates.

Keratoses with pigmentary changes—arsenic.

Pigmentation of the skin—arsenic, bismuth, silver salts.

RAT-BITE FEVER (Sodoku). (See page 652). It is a relapsing type of fever caused by the *Spirillum minus*. It is conveyed to man by the bites of rats, cats and other infected animals. The bite usually heals up and nothing further happens till 2 to 6 weeks afterwards, when the site of the bite becomes inflamed and there is some local lymphangitis. The temperature rises with rigor and prostration which lasts for 3 to 6 days only. Paroxysms of fever recurring at intervals of 5 or 6 days are characteristic features. With each paroxysm, there are rash, leucocytosis and eosinophilia.

Diagnosis. (1) History of a bite. (2) Peculiar temperature chart. (3) Animal inoculation with blood or gland. (4) Spirochaetes in the peripheral blood especially by dark ground illumination. (5) Leucocytosis (about 15,000) and eosinophilia. (6) Positive agglutination reaction to the spirillum. (7) Negative Wassermann reaction.

TREATMENT. (1) A course of six injections of novarsenobillon will cure the disease in doses of 0.3 to 0.45 gm., though one or two injections may cause disappearance of the parasites from the peripheral blood. The injections should be given at the onset of a spell of fever. (2) General and symptomatic treatment is also given. (3) Canterisation of the wound soon after the bite may prevent the infection.

REFRIGERATION. Refrigeration or thermosteresis is the process of abstracting heat or of making or keeping cool; when carried to its

limit, congelation or freezing ensues. The milder degrees are produced through the action of water of varying degrees of low temperature, applied in various ways. In more intense forms of refrigeration—congelation or freezing—volatile liquids like ether, ethyl chloride, etc., or of carbon-dioxide snow or liquid air are used. Local freezing causes an occlusion of blood vessels with subsequent anæmia, necrosis and atrophy of the epithelium in proportion to the intensity of the application.

Liquid air. Dried and purified atmospheric air is liquefied by repeated compression (at a pressure up to 2,000 pounds per square inch) and a cooling device. The temperature of the liquid air is -422.5°F (-252.5°C). It is marketed in what is called 'Dewar bulb', a flask so blown that one flask is inside another with a vacuum between. Liquid air is applied by means of pledgets of absorbent cotton wrapped around wooden applicators. In very small lesions a larger surface than would otherwise be necessary must be frozen because very small pledgets would not hold enough liquid.

Carbon-dioxide snow. The carbonic acid gas is liquefied under pressure (900 pound per square inch) with a cooling device similar to that used in liquefying air. When the liquid gas is allowed to escape its temperature falls to -23.8°F . (-31°C). To make snow for freezing purposes various methods are used. Hubbard apparatus is very convenient for the purpose. The temperature of the snow is -108.4°F . (-78°C), but it can be safely handled and moulded if the fingers are protected by chamois or leather gloves.

If liquid air could always be obtained it would be prepared because of the ease of its application, the rapidity of its action and its comparative painlessness. The uncertainty of the supply and its high cost make the use of liquid air almost prohibitive. The advantages of carbon-dioxide snow are: it can be easily obtained, it can be used on small lesions as, unlike liquid air, no larger surface than is necessary need be frozen as the mass or crayon of snow may be pared down to any size.

The indication for the use of carbon-dioxide snow: (1) to produce simple inflammatory reaction; (2) to produce destruction of certain tissues by interstitial scar tissue formation; (3) to produce immediate destruction of tissues by freezing. In affections of the skin carbon-dioxide snow has a wide range of usefulness. Lupus erythematosus, nevi, angiomas, chronic localised eczema, epitheliomas especially of the rodent-ulcer type, keratosis senilis, warts, papillomas, hypertrophied scars, keloid, etc., have all been cured by freezing.

RELAPSING FEVER. (See page 651). It is a febrile disease characterised by initial fever which ends by crisis in about seven days and is followed by a similar attack in about a week. The causal organism is the *Spirochæta recurrentis*, which is found in the blood during the pyrexial periods. Fever which is conveyed by lice is called

'Louse Relapsing Fever' and the fever which is conveyed by a tick is called 'Tick Relapsing Fever.'

DIAGNOSIS. (1) Clinically, the temperature chart gives a clue to the nature of the disease when a relapse occurs. Onset is acute with headache, pains in the body and vomiting. Spleen and liver are enlarged and tender. Jaundice may be present. (2) Examination of blood for spirochaetes during pyrexia: (a) fresh blood—by dark ground illumination, (b) dry film—stained by Leishman or India ink and (c) culture. Inoculation of blood into susceptible animals such as rats, squirrels, monkeys, etc. Spirochaetes appear in the blood of the mouse in about twenty-two days and persist for about two days. (3) The leucocytes are increased during the fever especially the large mononuclears. (4) Agglutination test is often positive. (5) Spirochaetes are often found in the urine.

TREATMENT. (1) Rest in bed. (2) An initial purgative (a dose of salts). (3) Novarsenobillon (0.4 gm.) intravenously when the temperature is rising. One injection is usually sufficient to prevent relapses but is advisable to give a course of 6 injections. If the injection is contra-indicated, stovarsol is given instead by mouth. Six tablets (4 gr. each) are given daily for two days.

RESPIRATION. The number of respirations in the resting adult is commonly about 17 or 18 per minute. This is influenced by various conditions of the body and also by age. A new-born child breathes about 14 times a minute, a child of five about 26 times, a man of twenty-five about 16, and of fifty about 18. The frequency is increased by any muscular effort even that of standing.

When breathing quickly, a man takes in and gives out at each breath about 500 c.cm. of air measured dry and at 0°C (*tidal air*). By means of a forcible inspiratory effort about 1500 c.cm. of air can be taken in (*complemental air*). At the end of a normal expiration a forcible contraction of the respiratory muscle will drive out about 1500 c.cm. more (*supplemental air*). *Vital capacity* is the sum of these three amounts and, is, on an average, about 3500 c.cm., i.e., it is the maximum amount of air that can be inspired after a powerful expiration. The *residual air* is the air which remains in the lungs after maximal expiration. It amounts to about 1,000 to 1,500 c.cm. *Alveolar air* does not refer to the air which is present in the anatomical alveoli, but is used to describe the air in the depths of the lungs, which is more or less in contact with the respiratory epithelium and can thus carry out gaseous interchanges with the blood. It is a physiological entity and consists of the supplemental air, and the residual air and amounts to about 3,000 c.cm. The *dead-space air* is found in the air passages, nasopharynx, trachea and bronchi. It does not carry out any interchange with the blood, and amounts to about 150 c.cm. The volume of the physiological dead space is not

constant but varies with the alterations in the state of the bronchial musculature and is increased in exercise.

Intrathoracic pressure. The pressure in the pleural cavity is sub-atmospheric and is 5 mm. Hg. during expiration, 10 mm. Hg. during inspiration. The pressure in the lungs is about 1 atmosphere as they are in free communication with the outside air. The negative pressure in the thorax is diminished by any factor decreasing the elasticity of the lung tissue. Thus, in an old man, where the elastic tissue is degenerated, the alveoli are enlarged, giving rise to a condition known as *emphysema*.

Chemistry of respiration. As a result of the oxidation processes associated with life and activity the tissues of a man of 70 kilo. body weight consume on an average during working hours about 400 c.cm. oxygen per minute. The tissues produce a large amount of carbon-dioxide. The oxygen required by the tissues is taken from the blood and the CO₂ formed is, in return, passed out in the blood. Hence the venous blood contains more CO₂. In the passage through the lungs the blood is arterialised, oxygen passing into it and CO₂ out, owing to an exchange with the air in the alveoli. The composition of the inspired and expired air compares as follows :

	Inspired air	Expired air
Oxygen	20.05 vol. per cent.	16.4 vol. per cent.
Nitrogen (including argon)	79.01 „ „	79.5 „ „
Carbon-dioxide ...	0.04 „ „	4.1 „ „

Under normal circumstances, inspired air contains a variable amount of aqueous vapour and has a variable temperature. Expired air is nearly saturated with aqueous vapour and in the trachea has approximately the temperature of the body, 37°C. The tension of aqueous vapour amounts to 47 mm. Hg. The oxygen tension of the alveolar air is 100 mm. Hg. and of CO₂, 40 mm. Hg.

By *respiratory quotient* is meant the ratio of CO₂ evolved to O₂ absorbed, and its absolute amount depends on the nature of food-stuffs or constituents of the body which are undergoing oxidation. If these were entirely carbohydrate the *respiratory quotient* (R.Q.) would be 1. If fat alone were being utilised it would be 0.71, with protein alone 0.81. In man on a mixed diet, the R.Q. at rest is somewhere about 0.85. The R.Q. is affected when the pulmonary ventilation is altered either voluntarily or secondarily to a rise of body temperature or fluctuation of the H-ion concentration of blood. (1) *Voluntary hyperpnoea* washes out excessive CO₂ and R.Q. may rise above one. (2) in *acidæmia*, there is hyperpnoea, and the R.Q. rises. The same applies to the rise of body

temperature. (3) In *alkalæmia*, the breathing is depressed, CO_2 is retained in the body and R. Q. falls. (4) During violent exercise, lactic acid enters the blood stream and breaks up the plasma NaHCO_3 and liberates large additional volumes of CO_2 ; the R. Q. then exceeds 2.

ARTIFICIAL RESPIRATION. Under various conditions the respiratory movements may stop and it may then be necessary to cause air to enter the lungs by some artificial means. The most controllable method by which air may be forced in and drawn out of the lungs at suitable intervals, is by means of air pumps, but when these cannot be used, quite efficient ventilation can be maintained by simpler means. The best method in man, is that described by Sharpey-Schafer. The subject is placed in the prone position, with the head slightly to one side, the mouth is cleared and the tongue pulled well forward. The operator, kneeling either at the side, or astride, places the palms of his hands flat on the subject's trunk just over or below the lowest ribs and then by leaning forward presses gently forwards and upwards for about two seconds. He then leans back a little to release the pressure for two seconds and repeats. In this way air is forced in and out and it is possible to maintain normal ventilation in an unconscious subject for long periods without undue fatigue on the part of the operator.

With patients under an anæsthetic for surgical operation and lying in the supine position, quite good results can be obtained by applying intermittent pressure on the epigastrium, by which means also the diaphragm is made to ascend. It cannot be too strongly insisted that pressure on the upper ribs is almost useless. In both of these methods, where possible, the subject is made to inhale a mixture of oxygen and 7 per cent. carbon-dioxide for the stimulation of the respiratory centre.

RESPIRATORY EFFICIENCY TESTS. The tests are difficult and complicated owing to close relationship of the cardiovascular and respiratory systems. These are of value in determining whether apparently healthy children or adults are up to the normal standard, whether young adults are fit for occupations involving a special strain on the respiratory organs such as flying, the strenuous exercises of athletes, etc. These tests also reveal diseases of the lungs and ascertain the degree of pulmonary damage in doubtful cases. The tests also determine whether persons are fit to stand operations on the chest or elsewhere in the body. *The vital capacity test.* This measures the maximum volume of air which is breathed out after a full inspiration. Thackrah examined the capacity of the lungs by using a large graduated glass jar, inverted over and filled with water. The person tested blew through a tube, the lower end of which was immersed in water under the jar. The largest vital capacity measured was 6,150 c.cm., the average for healthy men ranged from 3,600 to 6,000 c.cm. and for females about 2,160 c.cm. Hutchinsonson, using his spirometer, showed that the vital capacity is closely related to the standing height and modified by weight and age. A relationship also has been brought out between vital capacity and the surface area of the body, the

average for healthy males being 2,660 c.cm. per square metre of body surface. It is considered that the vital capacity of a person less than 90 per cent. of the normal is pathological. The statistics for vital capacity in normal healthy athletes give an average figure of 4,856 c.cm., the maximum and minimum being 5,750 and 4,000 c.cm. respectively. Flack gives a figure of 4,000 c.cm. as the average capacity for a fit flying officer. The vital capacity is lowered in diseases of the lungs and pleura and when the readings are normal, pathological changes in the lungs are usually not suspected. The degree of diminution of the vital capacity in pulmonary tuberculosis depends upon the activity of the disease rather than upon the extent of the lesion. Hutchison found that the vital capacity in the early stage of pulmonary tuberculosis is on an average 78 per cent. of the normal and in advanced stages about 38 per cent. and extensive pleural adhesions were not found to lower the vital capacity. The vital capacity is lowered in pleural effusion, lung abscess (16 per cent.), bronchiectasis (36 per cent.), asthma (34 per cent.), carcinoma of lung (50 per cent.), chronic bronchitis (32 per cent.), pneumothorax and cardiac enlargement (41 per cent.). *The manometer test.* Hutchison measured both the expiratory and inspiratory force of breathing by this test. The manometer is attached to the nose of the individual breathing in and out of the apparatus and displacing a column of mercury. The test is usually performed with the person tested sitting with the nose clipped and the height of the mercury column blown is noted. The abdominal muscles take part in the test. The average inspiratory pressure was found to be 51 mm. and the expiratory to be 63 mm. of mercury. Flack gives the average expiratory figure for a fit flying officer as 110 mm. Hg. The average figure of athletes is found to be 78 mm. Hg. The test does not afford any clue as to the presence of diseases such as bronchitis, emphysema or artificial pneumothorax. *The endurance or "Fatigue test."* Flack devised this test where the person tested blows up a column of mercury to a height of 40 mm. and sustains it there with the breath held as long as possible. The pulse rate is recorded every 5 seconds during the test. The test determines the efficiency of the expiratory muscles and the pulmonary circulation. Flack found that in a fit flying officer the column is sustained for 52 to 60 seconds and the pulse rate varies very little during the test. The average sustention time was found to be only 33 seconds. The figure however varies with individual cases. In respiratory diseases such as pulmonary tuberculosis, bronchitis, emphysema, bronchiectasis, asthma and pneumothorax the sustention time is lower than the normal figures. Strictly speaking the test is not of particular value, as a respiratory efficiency test. *Bronchial spirometry* has been unsuccessful because of its technical difficulties. Bluhm in measuring respiratory efficiency has considered both basal metabolic rate and blood circulation through the lungs; the latter is only affected when there is gross destruction of pulmonary tissue and not by pneumothorax or

thoracoplasty. The working test for pulmonary efficiency depends on the comparison of oxygen consumption after the performance of a standard amount of work. The subject of the experiment ascends flights of steps placed in a circle for 20 rounds, the rate of walking being fixed by a metronome at 88 steps a minute. The relative oxygen debt (Hill) is equivalent to the increase per minute in oxygen consumption following the period of work. Normal persons sometimes show little or no increase, but most results lie between 10 and 25 per cent. The test cannot be used for people who are confined to bed.

RHEUMATISM, ACUTE. It is an acute specific disease characterised by fever, pain in the joints and a special tendency to cardiac damage. It is one of the dreaded diseases specially of temperate climates and is rare in the tropics. The occurrence of the disease in the tropics is disputed though juvenile types have been reported in India. The disease has been found to exist in all its forms, namely, articular, cardiac and choreic. The articular form of the disease is mostly subacute in nature. The essential cause of the disease is obscure though it is an old-recognised one and has been described by Sydenham as far back as the seventeenth century. It was not until the year 1816 that the modern conception of the pathology of acute rheumatism was brought to light. Later on it was recognised that rheumatism was essentially a disease of childhood and girls are slightly more susceptible than boys. There is a well marked family incidence, but the most important known factor is environment, as acute rheumatism is a disease of the relatively poor, cold and damp were the first suggested causal factors. Chemical abnormality such as the accumulation of an excess of lactic acid or uric acid in the system has been suggested. The bacteriology of the disease started with Mantle's discovery of a diplococcus in the blood of a rheumatic child and later on Poynton and Payne after a series of most careful and consistent investigations discovered a diplococcus which was suggested to be the causal organism. It has been suggested that the lesions of rheumatism are not due to any specific organism and are not the result of a toxæmia but are really allergic manifestations due to a peculiar tissue reactions in certain individuals. The latest view is that of Schlesinger, Singy and Amis who believe that they have recovered a virus from cases of rheumatism in children.

The onset of the disease is abrupt and acute with a sense of chill and later on a rise of temperature. The temperature is usually remittent or intermittent in nature. Sweating is generally profuse and has a characteristic acid smell. The urine is scanty, high coloured and presents a trace of albumin on examination. Vague pains are complained of in the muscles and joints and are made worse by exercise and wet weather, and are usually relieved by warmth and sunshine. Of the joints affected, the knees and ankles are the commonest. The affected joints are swollen and red and synovial effusions may appear specially

in the large ones. The first definite sign of rheumatism in a child is cardiac involvement with a quickened pulse. The heart sounds change in character; the first sound at the apex becomes soft, blurred and accompanied by a systolic murmur and the second sound at the base may be intensified. As the heart adapts itself to myocardial damage enlargement of the organ of a permanent nature may appear. The blood shows considerable leucocytosis, sore throat is a constant accompaniment of the disease. A type of secondary anaemia is also seen among the victims.

TREATMENT. Three great essentials are recognised in the treatment. Absolute rest in bed should be enjoined from the onset of the disease to avoid excessive cardiac damage later on. The patient should on no account try to make any unnecessary effort or movement. In case of severe carditis the rest should be prolonged to months and the return to activity should be carefully graduated. The diet should be liquid during the acute stage of the disease and should include milk diluted with water, barley water, fruit juice, etc. The Imperial drink is very useful during the course of the disease. Intake of fluid should be free to compensate the loss of water from the body by sweat and to facilitate the excretion of the toxin from the system. A thorough search should be made for the detection of septic foci of infection in the body and when detected should be eradicated. At the same time the general condition of the patient should be improved. Of the reputed drugs, salicylic preparations deserve the name of specific remedies. The drugs cut short the course of the disease, cause the temperature to come down, lessen the inflammatory reaction of the joints. They also lessen the tendency to recurrences and sometimes cause the disease to abort at an earlier stage. The preparation most commonly used is the salicylate of soda. It should be given in sufficient quantities and should be evenly distributed in 24 hours. To a child of 10 years about 10 gr. of sodium salicylate can be safely administered every hour without any untoward symptoms intervening. During the regime, the child should be at complete rest, have a considerable amount of fluid to drink, a regular action of the bowels and be given twice as much of the bicarbonate as of the salicylate of sodium to prevent acidosis. About 180 gr. of sodium salicylate may be safely given to an adult patient in 24 hours. The quantity of the drug should be gradually cut down when the pain of the joints diminishes and the temperature comes down. There is an additional value in this method of treatment from the point of view of diagnosis, for if a patient suffering from acute arthritis with fever does not improve after 48 hours' treatment with full doses of salicylates, the case is certainly not one of rheumatic fever. Salicin is considered to be less depressing and is sometimes recommended for children. The old alkaline treatment has been incorporated with the salicylate treatment. In the earlier stages of the disease to relieve severe pain and induce sleep, nothing is better than the opium preparations. Antipyrine and

phenacetin should be avoided in children. Cases accompanied by hyperpyrexia may be treated by prompt application of a cold pack. During the active stage of the disease small blisters may be applied to the precordium and later on, iodide of sodium may be given internally. The administration of digitalis in cardiac cases is often attended with poor results. Strychnine, adrenalin and pituitary may be given if the blood pressure is very low. Recently blood transfusion has been advocated.

Bee venom has been found to be efficacious in the treatment of chronic rheumatism. It can be used in the form of an ointment for local application. Salicylic ointment is at first applied to the skin to render it more absorbent and then the ointment containing venom is used. The ointment is applied for 8 days, stopped for 4 days and continued for a longer period if necessary.

During the acute stage of the disease, the local treatment of acutely inflamed joints should comprise the use of splints for fixing the joints to ensure absolute rest and later on when the inflammation abates, careful massage attended with gentle passive movements should be encouraged. The use of the time-honoured oil of winter-green for massage of these joints should be resorted to. Convalescence is generally slow. A change of climate, rest, nourishing diet and tonics should be recommended for a speedy recovery.

SANDFLY FEVER. See page 969.

SCHISTOSOMIASIS. See page 332.

SCIATICA. See page 1414.

SEA-SICKNESS. The ætiology of sea-sickness is uncertain and complex. Various factors have been brought forward to explain its causation. The derangement of the labyrinthine function is considered to be the primary cause of sea-sickness. The symptoms associated with it are either secondary or accessory to the vestibular disturbances. Ketosis is a contributory factor; it sets in prior to the onset of vomiting and is relieved by combined glucose and alkali treatment. This predominating ketosis is also seen in subjects who have starved or undergone salicylate treatment prior to sailing. The sympathetico-tonic subjects suffer most from this condition; gastric stasis and pyloric spasm in them are both due to sympathetic over-action. Poor ventilation and high humidity also act adversely by increasing both the lassitude and headache so common in sea-sickness. Movements of the abdominal viscera like the derangement of the stomach with sinking sensation, nausea and vomiting and the changes of pressure affecting the liver by causing alternate congestion and anæmia are held to be probable causal factors in sea-sickness. The movement of the ship reinforces visceral reflexes and hence the use of an abdominal binder restricting movements of the viscera is advised. The unusual susceptibility of passengers to

the odour of the galley or of burnt engine oil on board-ship is one of the psychical factors responsible for the disease. External visual reflexes are also held to be potent factors.

TREATMENT. The pre-embarkation treatment should be started two to three days before sailing. It consists in administering cholagogue cathartics such as blue pill (4 gr.) overnight to be followed by a saline in the morning; diet should be plain and simple and alcoholic drinks are not to be indulged in to excess. Alkaline drinks with glucose should be freely taken to avoid ketosis. Susceptible passengers should take part in deck games, dancing and other forms of exercise having a general hygienic value. These modify the primary and secondary reactions in the disease. Here the object is to counteract the action of the vestibule by engaging other parts of the body in voluntary action. The prone position of susceptible persons in fresh air on the deck and well wrapped up against cold is generally beneficial. A tight abdominal binder or a bath towel kept in position by safety pins adds to physical treatment. Closure of eyes, wearing coloured glasses or bandaging one eye may be all helpful factors in the treatment of the disease.

Diet. Sometimes the thought, sight or suggestion of food is repellent to the patient. In such cases it is better to allow the patient to take any sort of food he likes and never to force him to eat. Alkaline drinks with addition of glucose are very beneficial in these cases, particularly in those where a tendency to vomit supervenes. Free fluid intake should always be encouraged.

Drugs. Of the sedatives, chlorotone, chloralamide, barbiturates and the bromides deserve mention, but the possible abuse of them should always be borne in mind and hence they should be only used in cases of necessity. Vertigo is a common and troublesome symptom in sea-sickness; luminal ($\frac{1}{4}$ gr.) is used as a vestibular sedative and may be given twice a day before embarking and should be continued for the first few days of the voyage. With the onset of symptoms, the drug is given hourly for four hours and the daily dose may then be increased to two or three grains for several days. The susceptible subjects are generally of the vagal type with a tendency to collapse and in these cases oxygen inhalation with vaporized ephedrine or adrenalin is very beneficial. Hypodermic injections of strychnine sulphate $\frac{1}{32}$ gr. and atropine sulphate $\frac{1}{100}$ gr. are also helpful in them.

SEROUS FLUIDS. Technique of exploratory punctures. (1) *Paracentesis thoracis.* The dull area, on percussion, is generally selected as the site for puncture. In extensive pleural effusions, the best site for puncture is in the mid-axillary line in the sixth interspace or in the eighth interspace in the posterior axillary line. The skin should be thoroughly sterilised with absolute alcohol or tincture of iodine. A local anæsthetic like 2 per cent. novocaine is injected and the skin along the

lower border of the upper rib is incised with a scalpel. Less than 1 inch of the needle of a sterilised 20 c.cm. syringe or a trocar (size 12 to 15) is pushed into the pleural cavity and care should be taken not to irritate the substance of the lung. With the same technique, the trocar from a Potaine's aspirator may be used for the purpose. Aspiration should be slow and it should be stopped if the patient gets a severe paroxysm of cough, pain or oppression in the chest, a feeling of faintness or expectorates blood-streaked sputum. After withdrawing the cannula or the needle of the syringe, a silkworm gut suture may be required if the skin wound is large or if it is a punctured wound it may be sealed with sterile cotton and collodion or tincture benzoin compound. The aspirated fluid, collected in a clean sterile and dry flask, may be sent for cultural examination.

2. *Puncture of the pericardium.* In cases of pericardial effusion, the fluid collects chiefly at the posterior and lower part of the cavity. The usual spot for puncture is the fifth intercostal space just outside the nipple line. This is usually $\frac{1}{2}$ to 1 inch inside the lateral border of relative dullness and no apex beat should be palpated at this point. With the same aseptic precautions as for draining the pleural cavity, the trocar is slowly pushed in, tilting it upward and medially towards the apex of the heart. In cases of marked effusion, as much as 200 to 500 c.cm. of pericardial fluid have been removed. The procedure is said not to be attended with much danger but drugs such as strychnine, atropine, adrenalin, etc., should be at hand for emergency use.

3. *Paracentesis abdominis.* The best site for puncture of the abdominal wall for withdrawal of ascitic fluid is midway between the umbilicus and the pubes. The bladder should, in all cases, be empty and the patient should be in a sitting posture. Aseptic precautions and other procedures are the same as in thoracentesis. The fluid should slowly drain through the cannula and the patient should have a tight abdominal binder around the abdomen as soon as the fluid leaves the abdominal cavity. The danger of the operation lies in injuring a coil of intestine, which is very rare.

Examination of the aspirated fluid. Non-purulent fluid. (1) Specific gravity can be determined by the urinometer. (2) Sero-mucin test of Rivalta. One drop of glacial acetic acid is added to 100 c.cm. of distilled water and 1 or 2 drops of the puncture fluid is poured into it. If the fluid is an exudate, a bluish-white cloud appears and if a transudate, no such cloud appears. A positive Rivalta reaction is seen in pneumothorax. (3) *Cytodiagnosis.* Citrated or oxalated fluids are preferred to clotted specimens. The fluid is centrifuged for about 10 minutes and a drop of the sediment is uniformly spread in a thin layer over a clean and dry glass slide. Methylene blue or Wright's stain is used to stain the smear. A differential count of lymphocytes, endothelial cells and polymorphonuclears, may be made as in a blood film. Tuberculous effusions are usually non-purulent with lymphocytes

predominating. The bacilli are never detected by ordinary microscopic examination of the smear. Culture, in Corper's crystal violet potato medium, of the sediment of a centrifuged specimen, in a suspected case, gives a satisfactory growth of the tubercle bacilli in two weeks to two months. Biological test consists in injecting the sediment into the groin of two guinea pigs. Guinea pigs develop tuberculosis in one to three months.

Characters of the aspirated fluids. (1) Clear serous transudate is light yellow or greenish in colour with specific gravity below 1015 and albumin content under 3 per cent. The Rivalta reaction is negative and the stained smear of sediment shows few cells, mostly endothelial and no bacteria. (2) Serofibrinous exudate is yellow in colour and cloudy due to the presence of fibrin with specific gravity above 1018. The Rivalta reaction is positive with albumin content over 3 per cent. Microscopical and cultural examinations of the smear and centrifuged sediment are of importance in these cases. Infection with tubercle bacilli is highly suggestive where lymphocytes predominate and here cultural examination and animal inoculation of the centrifuged sediment are of immense value. The presence of an overwhelming number of polymorphonuclears strongly suggests an early pyogenic infection. A cultural examination should be undertaken to demonstrate influenza bacilli, streptococci, pneumococci, etc. (3) Purulent fluid. Here a Gram-stained smear shows pus cells, pneumococci, streptococci and staphylococci. If a direct smear shows no bacteria, culture for tubercle bacilli.

Rarer fluids. (1) *Syphilitic fluids.* Smears show equal numbers of lymphocytes and endothelial cells. The Wassermann reaction is positive on both the fluid and blood. (2) *Fluids in hydatid disease.* The fluid is clear with proteins less than 1 per cent. and specific gravity below 1010. Microscopic demonstration of the typical curved hooklets in the centrifuged sediment confirms the diagnosis. (3) *Chylous fluids.* The true form is due to erosion of lymphatic channels by filarial parasites, malignant growths, tubercle bacilli and Hodgkin's disease. The fluid has a smell of fatty foods. The pseudochylous fluid is thought to originate from an albuminous degeneration of the endothelium, the exact mode of production being unknown and is met with in chronic nephritis, tuberculosis and malignant growths. It is pure white in colour and has no characteristic smell. (4) *Hæmorrhagic fluid* is of rare occurrence and is met with in cases of thoracic aneurisms, pulmonary tuberculosis, hæmorrhagic diseases and trauma.

SYNOVIAL FLUID. Normal characters. It contains about 50 white cells per c.cm. with a differential count of polymorphonuclears + 5 per cent., monocytes + 58 per cent., macrophages + 30 per cent. and endothelial cells + 8 per cent. A few red cells are found in the fluid in recent traumatic cases and the icterus index is over 6.

Collection of fluid for examination. The skin of the most dependent part of the fluctuating swelling should be thoroughly swabbed with tincture of iodine to make it aseptic. A sterilised 20 c.cm. record syringe is used to withdraw the fluid. A local anæsthetic like ethyl chloride or 1 to 2 per cent. novocaine may be used before the puncture is made. The fluid is examined for: the leucocyte count, an icterus index estimation, Wassermann reaction, estimation of sugar content, pH estimation and cultural examination. Direct smears do not show tubercle bacilli or gonococci even if the infection is acute.

SNAKE-BITE. See page 1079.

SORE-THROAT. *Diphtheritic cases.* The diagnostic features are: The knee-jerks are liable to disappear and albumin is often present in the urine, these are very early manifestations of the disease. The character of the patch should always be observed. Frequent throat swabs are to be taken for bacteriological examinations. The sub-maxillary glands are often enlarged on the affected side only while in non-diphtheritic cases they are bilaterally enlarged.

In diphtheritic cases give the patient a mixture containing biniodide of mercury. The following is a convenient way of prescribing it: Perchloride of mercury 1 gr., potassium iodide 30 gr., glycerine 2 dr. and water to 8 oz. Each ounce of the mixture contains less than 1/8 gr. of perchloride of mercury and a tablespoonful is a perfectly safe dose for an adult. The glycerine is added to make the mixture adhere to some extent to the fauces and thus secures a local as well as a constitutional effect. The biniodide of mercury is also a very powerful bactericide and is especially inimical to the Klebs-Löffler bacillus. For detailed treatment see pages 799 and 1343.

Acute tonsillitis. The common recognised types are acute catarrhal, lacunar, and parenchymatous. It may be a primary infection or secondary to nasopharyngeal infections. The causal organism is generally a hæmolytic streptococcus.

TREATMENT. Swab both the tonsils all over with tincture of iodine (not Mandle's pigment). Spray the throat with hydrogen peroxide in warm water (1 in 4) or a warm alkaline spray or douche with a Higginson's syringe, a solution containing carbolic acid 1 gr., sodium bicarbonate 5 gr., and water to 1 oz. Internally, sodium salicylate or aspirin 5 gr. each, may be given every four hours or a powder containing salol 5 gr., phenacetin 3 gr. may be given every two hours. Small doses of aconite often bring the temperature down. A useful prescription is tincture of aconite 1 min., antipyrin 1 gr., caffeine citrate 5 gr., and water to 1 oz., one dose to be taken every hour till six have been taken.

PERITONSILLAR ABSCESS (Quinsy). Strictly speaking, this is a suppuration of the tissue of the soft palate outside the capsule of the tonsil, but many of them are actually intratonsillar ones. The palate is

congested and bulged; there is also pain, with dysphagia and high temperature.

Treatment. It is surgical and indicates evacuation of the pus contained in the abscess.

VINCENT'S ANGINA. This is an infection of the tonsils by the fusiform bacillus and a spirillum; deep ulceration of the tonsils is a marked feature. There is sore throat on one or the other side, the temperature is not high and the mouth has a characteristic unpleasant foetor. For diagnosis a bacteriological examination of a throat swab is necessary.

Treatment. Gargles and throat sprays containing hydrogen peroxide in warm water to which a teaspoonful or two of glycothymoline is added are very useful. Local application with a swab of fresh salvarsan or neosalvarsan powders applied 2 to 3 times a day to the ulcerated parts is most beneficial. Application of equal parts of ipecacuanha and Fowler's solution is also useful. Local applications of perborate of soda, methylene blue, and trichlor-acetic acid are also used. For obstinate cases, intravenous injections of neosalvarsan are indicated.

Other causes of sore throat are: acute septic pharyngitis, hospital sore throat, Ludwig's angina, herpes of the pharynx (rare) and pemphigus. These are treated on the lines indicated above.

SPRUE. See page 879.

SPUTUM. *Collection of the specimen.* As secretions of the naso-pharynx and mouth are likely to contaminate the sample, it is desirable as a preliminary measure to cleanse the mouth with some antiseptic lotion. It should be coughed up into a sterile wide-mouthed bottle and submitted for ordinary microscopical and cultural examinations. The sample should be examined within two hours of such collection. In case of a child, washings from the fasting stomach may be examined for tubercle bacilli or the child may be induced to cough by tickling the throat and the particle of phlegm may be swabbed off from the posterior pharyngeal wall.

GENERAL CHARACTERS. (1) *Amount.* In measuring the twenty-four hours' sample, the quantity of supernatant saliva and other secretions should be deducted, leaving behind the purulent material only. From 4 to 20 oz. of sputum are expectorated in case of bronchiectasis, discharging abscess and pulmonary tuberculosis with cavity formation. As the lesion in the lungs heals up, the amount of sputum brought out also decreases but the latter gives no idea of the extent of pulmonary disease. (2) *Odour.* Ordinarily sputum is odourless. It has a very foul offensive smell in cases of lung abscess, bronchiectasis, tuberculous cavities and particularly in gangrene of the lungs. (3) *Types.* (a) Mucoid sputum is transparent and glairy and is met with in most acute pulmonary infections and after attacks of bronchial asthma. (b) Mucopurulent sputum consists of masses of opaque pus of varying colour, floating in mucus. The purulent material is increased and

marked in bronchiectasis, pulmonary abscess and tuberculous cavities. Pus and mucus are intimately mixed in cases of pulmonary abscess. (c) Distinct purulent sputum is found at the height of acute infections of the respiratory passages and particularly in bronchiectasis cases. If expectoration of homogenous material is sudden and acute, it is a case of ruptured abscess of the lung or empyema. (4) *Layer formation* of sputum is characteristic in bronchiectasis, lung abscess and gangrene. The topmost layer is one of frothy pus, the intermediate is of watery mucus and the lowest layer consists of pus. (5) *Blood-stained sputum*. Expectoration of blood-stained sputum, though highly suggestive of a grave pulmonary lesion, should never be confirmed unless the surrounding regions such as the mouth including the gums, nasopharynx, etc., are thoroughly investigated. The prognosis is usually grave if the amount of blood brought out exceeds one drachm. In hæmoptysis, the blood is bright red and frothy and the sputum is tinged with blood for days together even after the cessation of hæmoptysis. Microscopical demonstration of tubercle bacilli or a large number of spirilla in sputum confirms the diagnosis. Moreover, the sputum will also contain pus in cases of bronchiectasis, lung abscess, gangrene, etc. A radiogram of the chest in these cases also helps the diagnosis considerably. In old people carcinoma of the lungs should be borne in mind.

MICROSCOPIC EXAMINATION OF SPUTUM. The examination of an unstained film under the low power lens of a microscope is important as it gives much valuable information. The film should be moderately thick. A drop of strong caustic soda will liquefy purulent material of the sputum and will facilitate the demonstration of elastic fibres, ray fungus, blastomycetes, heart-failure cells, dust cells, Curschmann's spirals or Charcot-Leyden crystals. The presence of *elastic fibres* has prognostic importance. These indicate damage of pulmonary tissues and are abundantly found in progressive pulmonary tuberculosis, ulcerating bronchiectasis, abscess and gangrene. The sputum is boiled with an equal volume of 10 per cent. sodium hydroxide, centrifugalised and the sediment is submitted for microscopical examination. *Fungi* such as streptothrix, leptothrix, the actinomyces, are sometimes accidentally found in the sputum of patients suspected clinically to be suffering from pulmonary tuberculosis. The symptoms of such patients clinically resemble those of tuberculosis but the sputum shows no tubercle bacilli. The *heart failure cells* are phagocytic histiocytes from the alveolar walls of the lung. They are large cells with the nucleus situated eccentrically and containing yellow granules. The sputum in these cases is brown due to the presence of pigments, hæmatoidin and hæmosiderin. They are abundant in pathological cases only, such as, mitral stenosis and pulmonary infarcts. The *dust cells* are found in the brownish-black sputum of people living in the dusty atmosphere of big cities. These look like heart-failure cells and the pigment is due to carbon particles. The *Curschmann's spirals* are dense fibres of mucus which appear in

the sputum only after asthmatic attacks, though eosinophilia is more diagnostic in these cases.

DEMONSTRATION OF TUBERCLE BACILLI. Technique of staining a film. The smear should be moderately thin. Carbol fuchsin should never be boiled but should be heated till it steams. The stain is then poured over the slide to cover the smear. After three minutes, the stain should be washed off with water. It is then decolourised with acid alcohol (concentrated hydrochloric acid 3 c.cm. and alcohol 95 per cent. 97 c.cm.) until it is pinkish-gray on washing with water. Loeffler's methylene blue is used as a counterstain and kept for half a minute. It is then washed with water, dried and examined for tubercle bacilli under the oil immersion lens of the microscope. Under the microscope the bacilli appear as small red rods, a few are curved and others are slightly beaded. The presence of bacilli of this nature is diagnostic, but in the event of none being seen, several smears should be examined. When sputum is not available, throat swabs and gastric washings should be examined for bacilli.

Culture and animal inoculation of sputum for diagnosis of tuberculosis. Ordinarily stained smears of sputum do not show tubercle bacilli if these are less than 100,000 per c.cm. of sputum whereas the presence of 10 to 100 bacilli per c.cm. of sputum produces a positive culture or tuberculous lesions if inoculated into a guinea pig. The medium used in cultural methods is 0.5 c.cm. of sterile citrated blood or 0.5 c.cm. of fresh egg yolk treated with 6 per cent. sulphuric acid. The sulphuric acid destroys all bacteria except tubercle bacilli. After incubation of sputum at 37°C. for 45 minutes, the sulphuric acid is neutralised with sterile 1.3 per cent. sodium bicarbonate in 3 per cent. glycerine. The growth is watched at weekly intervals for three weeks till positive culture is obtained. A smear of such a culture may be stained with carbol fuchsin to demonstrate tubercle bacilli under the microscope.

Whooping cough organisms in sputum (early diagnosis). The special culture medium used is the glycerine-potato-blood agar medium of Bordet-Gengou with a pH 5. A small Petri dish is held vertically before a child's mouth during a coughing attack. The cough should be deep and expulsive. Droplet infection of the medium in the Petri dish takes place and the plate is incubated for 48 to 72 hours. *Bacillus pertussis* colonies appear as tiny pearls surrounded by dark zones. Under the microscope, a smear, when stained, shows Gram negative small organisms resembling pneumococci. The organisms are generally detected in the catarrhal stage of the disease at a period of greatest infectivity.

Vincent's organisms in sputum. Collection and technique of staining. In all chronic pulmonary diseases, sputum should be examined to detect Vincent's organisms. Thorough aseptic precautions of the mouth including the gums, teeth and tonsils should be taken before the collection of the sample and the specimen should in all cases be

examined within half an hour of collection. The smear should be thin and free of purulent materials. It is stained with steaming carbol fuchsin for three minutes. The stain is then washed off, dried and the film submitted to microscopical examination. The bronchial spirochætes, if present, appear as pinkish red organisms. Negative findings have no value and even in positive cases, contamination from the oral cavity should be borne in mind. In pathological cases they are present in numbers as secondary invaders and are commonly met with in chronic bronchopulmonary diseases and pulmonary hæmorrhage.

Pyogenic organisms in sputum. Gram's stain is used in finding the organisms in acute infections. The organisms commonly found are pneumococcus (Gram positive); Friedlander's bacillus (Gram negative); streptococcus (Gram positive); micrococcus catarrhalis (Gram negative); influenza bacillus (Gram negative); Bordet-Gengou bacillus of whooping cough (Gram negative); these appear as tiny bacilli resembling influenza bacilli.

STOOLS. *Functional test for gastro-intestinal motility.* The patient swallows a 10 gr. capsule of carmine and the stool is watched for a change of colour. It should normally become coloured red in 24 to 48 hours and the colour should continue for 48 to 72 hours after taking the carmine capsule.

Collection of fæces. About half an ounce of formalin should be added to the collected stool to destroy the disagreeable odour. For cultural examination and detection of occult blood in the fæces, formalin should not be added.

GENERAL CHARACTERS. *Colour.* The normal colour of stools varies from yellow to brown. Pale-coloured stools indicate poor digestion with deficiency of bile and pancreatic secretions. The colour also varies due to intake of different foodstuffs and drugs. Tarry-coloured stools are found in lesions of the upper gastro-intestinal tract. Fæces tinged with fresh red blood indicates a lesion in the lower gut and particularly of the rectum. *Form.* Normal stools should be semi-formed with undigested food particles in them. Loose stools indicate deficient absorption of the fluid matter from the faecal mass in the large intestine or a rapid evacuation of the intestinal contents. Narrow and ribbon-like stools indicate a spasmodic condition of the gut. Scybalous masses are the result of a spastic condition of the colon. *Mucus and pus.* A naked eye detection of mucus and pus in the fæces indicates colitis or enteritis. In acute diarrhoeas, mucus is intimately mixed with faecal matter. Pus in stools is usually found in inflammatory conditions of the gut. *Chemical tests:* *Occult blood.* Benzidine-acetic-acid solution is the reagent ordinarily employed for the test. It is prepared by dissolving powdered benzidine in 3 c.cm. of 80 per cent. acetic acid. A small portion of the fæces is smeared on the centre of a white paper and a drop of the reagent is poured over it. The development of green or blue colour in less than one

minute indicates the presence of blood in the stools. A deep blue colour within 3 seconds indicates over 5 per cent. of blood; a pale blue colour in 3 to 5 seconds indicates 1 to 5 per cent. of blood; a pale blue or green colour within 15 to 60 seconds indicates less than 1 per cent. of blood and a pale blue colour after 30 seconds is of doubtful value. Another most sensitive test to detect occult blood in faeces is to use a saturated solution of benzidine in glacial acetic acid with hydrogen peroxide. It is added to a boiled solution of faeces when the blue colour develops. The test will give a positive reaction to blood in a dilution of 1 in 3,000,000. Unlike the former test, dietary precautions are to be observed in these sensitive techniques as this is likely to yield false results. Extra-gastro-intestinal sources of bleeding should be looked for and excluded before a test is done and a diagnosis given. Repeated examinations of stools are helpful in these cases to confirm a diagnosis. The test is positive in cases of peptic ulcers, carcinoma of the gastro-intestinal tract, ulcerative colitis, dysentery, typhoid fever, intestinal tuberculosis, acute abdominal emergencies such as mesenteric thrombosis, volvulus and intussusception, cirrhosis of the liver and general hæmorrhagic diseases such as purpura, scurvy, leukaemias, etc. *Biliary pigments.* The reagent used in the test is a saturated aqueous solution of mercuric chloride (mercuric chloride 101 gr. in 4 oz. of distilled water) or concentrated nitric acid. To a quantity of faeces about 3 to 4 times its volume of mercuric chloride solution is added and the two are mixed with a glass rod. The development of red colour denotes hydrobilirubin (urobilin) and a green colour, bilirubin. The colour generally appears in less than an hour but may require more time if the quantity of bile is small. Urobilin, the decomposed product of bilirubin, is the normal pigment of faeces. The test is required to ascertain the amount of bile present in the stools. Absence of bile gives rise to bulky, offensive, pale-coloured stools.

MICROSCOPIC EXAMINATION OF STOOLS. The smear on a glass slide should be from a fresh specimen and mixed with an equal amount of water. The film should be a thin one. The objects seen under the microscope are: vegetable fibres; spirals or cells; triple phosphate crystals; connective tissue strands and muscle fibres; epithelial cells and leucocytes; worms and their ova; occasionally amoebæ and flagellates; red blood cells and bacteria. For details of examination of faeces for intestinal parasites and their ova see page 1384.

INFANT'S STOOLS. The following should be noted: (1) *Number.* More than 4 evacuations should be considered pathological. (2) *Colour.* Normal colour is brown but infants fed solely on milk have pale yellow or green stools. Green stools in diarrhoeas indicate that the bile could not undergo a change in the gut. (3) *Consistency.* It varies and depends on the nature of feeds given to the infant. Foamy stool is due to carbohydrate fermentation. (4) *Odour.* A sour odour is due to carbohydrate fermentation while a foul putrefactive smell indicates protein

putrefaction. (5) *Curds*. The appearance of curds in infant's stools is thought by some to be normal. Protein curds are hard, tough and leathery; fat curds are buttery in consistency. (6) *Mucus*. It indicates an inflammatory condition of the gut and the amount varies with the severity of the lesion. (7) *Blood*. Intimately mixed with fæces and associated with loose stools, blood is seen in cases of infectious diarrhoea, dysentery, ulcer, intussusception, tuberculosis and scurvy. Stools smeared with fresh blood outside indicate a lesion of the rectum such as fissure, ulcer, polypus, etc.

CULTURAL EXAMINATION. Cultures from fresh specimens only are desirable. Nutrient broth is the medium used for it. The pathogenic organisms found are *B. dysenteriae* of Sonn, Flexner, Hiss, Russell, *B. paratyphosus* B and C; *B. morgani paracoli*; *B. dysenteriae*, schmitz, etc.

PARASITES AND THEIR OVA IN THE STOOLS. The examination of stools is never complete unless a naked-eye examination for a part or whole of a parasite (*e.g.*, tænia and oxyuris) or their larvæ (*e.g.*, strongyloides) or a microscopical examination for their ova is undertaken. In positive cases, detection of parasites may be difficult at times but the ova are generally present in all specimens submitted for microscopical examination. In anæmic patients particularly, the examination of the stool for parasites and their ova should be a routine procedure. *Collection and examination of fæces*. The specimen for examination should be collected in a wide-mouthed bottle with a little addition of formalin and water. The formalin destroys the disagreeable odour and dilution with water helps emulsification of the sample facilitating the detection of ova under the microscope. To search for the adult worms, *e.g.*, tapeworm segments and oxyuris, it is advisable to give a dose of salts at night and examine the stool the following morning. The liquid stool is poured on to a sieve and water poured on it; the fæcal matter is washed away leaving the worms and undigested residues of food. The contents of the sieve are transferred to a black or dark-brown dish or simply a large Petri dish with a piece of black paper underneath, when the worms, if present, can be easily picked up. *Microscopical examination*. To examine stools for ova, it is desirable not to administer any purgatives, as ova are better demonstrated in formed stools than liquid one. *Simple smear*. A thin smear of stool is made on a clean dry glass slide and the whole area is examined under the low power lens of the microscope. Ova and larvæ are seen, when these are present in overwhelming numbers.

McVall's method. The method is generally adopted for hookworm ova. A thick smear of stool with water is made on a glass slide and left for five minutes. The whole is then gently immersed in a bowl of water. The floating coarse particles and debris are washed away, leaving the ova on the slide.

Willis method. About half a gramme of fæces is poured in a small tin container and a thorough emulsion of it is made with saturated salt

solution. The container is filled to its brim with salt solution and a clean glass slide is put over it in contact with the stool emulsion for nearly ten minutes. The slide is rapidly lifted up and then examined under the low power focussing on the upper surface of the film and not on the slide. Almost all nematode ova (excepting unfertilised ascaris ova) float in saturated salt solution and hence are present in the film on the slide. This method is not useful for detecting strongyloides larvae unfertilised ascaris ova and ova of flukes and tapeworms.

Rivas method. About 2 gm. of stool is emulsified in 10 c.cm. of 5 per cent. acetic acid solution. The homogenous suspension is allowed to settle for two minutes; 5 c.cm. of the supernatant fluid is removed with a pipette and an equal quantity of ether is added to it. It is then centrifuged. Four layers of ethereal extract, detritus, acetic acid and sediment are formed in succession. The layers of ether, detritus and acetic acid are carefully poured off and the sediment at the bottom of the tube is submitted for microscopic examination.

Direct Centrifugal Floatation or D.C.F. method. This delicate method has been devised by Clayton Lane to detect hookworm and other ova which float in saturated salt solution and is of special value for diagnosing mild infections. The stool is first emulsified in water and centrifuged. Saturated salt solution is then added to the sediment and the tube filled to the brim with the solution. A special square cover-glass is placed on the top of the tube touching the salt solution and is held in place by four horns of the specially designed centrifuge bucket. The tube is centrifuged again at high speed and the cover-glass is lifted off and placed on a slide on two little plasticine cones with the film side downwards like a hanging drop preparation and is examined under the low power of the microscope.

SUDDEN DEATHS. Apart from sudden deaths after violence, accidents and poisoning, the statistics of the different pathologists of the world show that the majority of such accidents is due to sudden stoppage of the heart, profuse hæmorrhage from various causes and arterial embolism and thrombosis in different parts of the body. Of the diseases of the heart, valvular diseases including the aortic and the mitral valves, atheroma of the coronaries, syphilitic involvement of the coronaries, myocardial fibrosis, fatty infiltration, cardiac failure from high blood pressure, aneurysms of the aorta, both ruptured and unruptured, account for a large number of cases. Respiratory diseases including hæmoptysis in pulmonary tuberculosis, cancer of the lung, obstruction of air passages due to foreign body, diseases like diphtheria, malignant growths like carcinoma, pneumonia, pulmonary embolism are responsible for others. Other common causes include intracranial hæmorrhage, intracerebral hæmorrhage, tumours of the brain, oedema of the brain, ruptured cerebral aneurism, brain abscesses, cerebral embolism, acute infections and septicæmia, heat stroke, heat exhaustion, operative shock, allergic

and anaphylactic shock, deaths during anæsthesia, abdominal emergencies such as perforated peptic ulcers and perforated appendix with peritonitis, obstruction, etc.

SYPHILIS. This is a specific disease of wide distribution caused by *Treponema pallidum* (*Spirochæta pallida*). It may be acquired where the causal organism is propagated by inoculation or conveyed from person to person by contagion or it may be inherited where the disease is conveyed to the child by either or both the parents. The treponema of syphilis is a spiral curved organism 5μ to 15μ in length and is actively motile in fresh specimens. It survives for a short time only outside the body and is killed by weak antiseptics. The parasite has been cultivated by Noguchi; no race is known to be immune from the disease but infection confers immunity to a great extent and in fact a second attack is unknown in untreated cases.

In the majority of cases the disease is transmitted by sexual union (90 to 95 per cent.) though the term venereal disease strictly speaking is not correct as there are other modes of inoculation (5 to 10 per cent.). Accidental infections are known to occur in surgical and obstetrical practice. A characteristic local sore may not appear and a chancre on the lip or fingers affords the most common example of the extragenital variety. Wet nurses are very often infected on the nipple and relatives of a syphilitic child may be similarly accidentally infected. The treponema gains entrance to the body through a small break in the continuity of the skin or the mucous membrane. In acquired syphilis the chief site of infection is the genito-urinary tract; less frequently on the mucous membranes or mucocutaneous junctions such as the lips and rarely on the unbroken skin surface. After inoculation the organisms multiply at the site and produce a chancre, a manifestation of slowly developing tissue reaction. The organisms spread to other sites of the body by the perivascular lymphatics from the original infected site and afterwards multiplying further, they are carried to the various tissues or organs of the body through the blood.

Incubation period is from ten days to ten weeks and on an average is about three weeks. There is a general infection of the body within a few days of inoculation possibly within twenty four hours. If untreated, the primary lesion lasts from 3 to 4 weeks and the healing of the lesion occurs with marked induration of the part. The serum from the primary chancre contains a considerable number of spirochætes and the organisms may even be found in the scars of the primary lesion. A generalised infection becomes apparent after an interval of 6 to 8 weeks. Manifestations in such cases may be severe or be very slight. Evidence is entirely lacking whether the body can overcome the infection entirely by its own resistance. The acute secondary stage lasts for several months but rarely a year and the

manifestations in some cases disappear for ever while in others only for varying periods.

Clinical features of acquired syphilis. The chancre or the primary lesion appears after the incubation period. Though these chancres have certain characteristic features it is difficult to diagnose the disease at this stage from clinical features only and microscopic examination is necessary. On an average in about three weeks from the time of appearance of the chancre, the blood becomes positive to Wassermann reaction though it may be positive earlier, and for treatment and prognosis it is usual to classify cases as of those with sero-negative W.R. and those with sero-positive W.R. The classification of syphilis into 3 or even 4 stages is becoming obsolete because it is now known that no one stage is characterised by definite group of symptoms nor there is any line of demarcation from one stage to the other. At any time from about one month to several months after the appearance of the chancre but usually about six weeks from the time of appearance of the sore there appear the manifestations which are called secondary syphilides. Along with these, there may be mild constitutional symptoms such as fever, malaise, headache and generalised pain all over the body. The commonest manifestations during this time are those on the skin and the mucous membrane. Skin lesions are dull red or copper coloured, circular or oval in shape with indurated margin and there is absence of itching. The organisms of syphilis are found in the serum exudate of these lesions and Wassermann reaction of the blood is almost always positive. The types of skin eruptions are varied in character and these may be macular, papular and papulo-squamous; pustulation is not common. Different varieties are present at the same time and this polymorphism is characteristic of the disease. During the early stage of eruptions, these are distributed all over the body in a symmetrical form. Mucous patches and moist papules are also met with at this stage of the disease at particular regions of the body. The mucous membrane of the mouth and tongue may be involved. Condylomata about the genitalia and moist papules are seen in persons with unclean personal habits. The late secondary manifestations are of papulo-squamous type; some are nodular lesions in the skin like tuberculoma or psoriasis and in comparison with earlier lesions these are not symmetrical. Another characteristic but not common lesion at this stage is leucoderma of the neck specially found in young females with dark hair. With treatment these symptoms disappear quickly, but even when untreated they disappear in time. With the subsidence of the secondary syphilitic manifestations the disease passes into a latent stage. During the latent period usually extending to a few years the only evidence of the presence of the disease is the generalised enlargement of the lymph nodes and a positive Wassermann reaction of the blood.

In the next tertiary stage, the slow infiltrating lesions usually of the cardiovascular system are met with. The gummatous lesions of the skin and subcutaneous tissues are formed. These are painless swellings ultimately breaking down in the centre and giving rise to ulcers with punched out edges and wash leather bases. The periosteum of the bones is thickened and sclerosis is marked. The main viscera involved during this stage in addition to heart and blood vessels are the liver, the kidneys and the stomach; other viscera are also involved though very rarely. Any structure in the body can be affected during this stage. Neurosyphilis was considered to be the terminal stage of the disease, but it is now clear that the central nervous system may be involved any time, even during the early stage of the disease. The affection of the central nervous system is slow and insidious and symptoms manifest themselves late. The examination of the cerebro-spinal fluid is advised in all cases of early syphilis from six months to one year's time and in late cases before any treatment is started or as early as possible thereafter. According to the anatomical structures involved neurosyphilis may be meningeal, vascular, hemiplegic, monoplegic, aphasic, parenchymatous, (G. P. I., tabes dorsalis, meningo-vascular gumma of the brain, spastic paraplegia); in many cases one may merge into another.

Congenital syphilis. In case of congenital syphilis, the foetus is infected by the passage of the treponemata from the maternal circulation through the placenta. It is rare to find an infected foetus before the fourth or fifth month of gestation and this is an important fact in connection with the treatment of infected mothers in pregnancy and also in antenatal work in getting children free from syphilis out of infected mothers. The possibility of a child being infected in utero lessens as the years increase between the birth of the child and the time the mother got infected (Kassowitz's law). The disease may lead to mis-carriages, premature birth and of birth of still-born infants. Sometimes a living child may be born which dies in very early life (within two years). Subsequently a child may be born with evident manifestations of syphilis or may be born without any outward signs or symptoms but may later develop symptoms. There is no primary stage in congenital syphilis. Lesions ordinarily met with are fissured ulcerative lesions of the skin near about the mouth, genitalia and anus; snuffles or serous or mucopurulent discharge containing treponemata which is highly infectious; bullous skin eruptions chiefly met with about the buttocks, soles and palms; epiphysitis; enlargement of the liver and spleen. Near about the age of 7 or 8 years or even later interstitial keratitis is very suggestive of congenital syphilis. Other classical signs are undue prominence of the frontal or parietal bones, eighth nerve deafness (detected often by marked shortening of bone conduction while air conduction remains very acute), high arched palate, saddle nose, Hutchinsonian teeth, peg-shaped upper central incisor

teeth with or without notching and involving the permanent teeth only and sabre-shaped tibia.

Hutchinson's triad, diagnostic of congenital syphilis, are interstitial keratitis, deafness and pegging of the incisor teeth. Visceral lesions are less common in congenital syphilis though involvement of the liver and spleen is met with, cardiovascular involvement is almost absent in congenital syphilis; the central nervous system is affected like the acquired type. It must be remembered that congenital syphilis is easily preventable if treatment of the pregnant mother is carried out in time.

TREATMENT. The treatment of syphilis should be started immediately the diagnosis is made. It is now generally realised that the earlier the course of treatment is started the better are the chances of a permanent cure. Early treatment is also of value in cutting short the period of infectivity as it has been found that *T. pallida* cannot be demonstrated in a lesion twenty-four hours after an arsenobenzol injection. Again it should be remembered that mere disappearance of the signs and symptoms of the disease does never guarantee a cure. The treatment should therefore be an intense and prolonged one as soon as a definite diagnosis is made as it is difficult to gauge with accuracy the ultimate effect of courses of treatment served. Harrison advocates a treatment with both arsenobenzol and mercury for some time after the blood sera gives a negative Wassermann reaction. Mercury being a comparatively feeble antisypilitic drug, reliance cannot be wholly made on it without arsenobenzol compounds. Mercury may well suffice for a continuation treatment after a thorough course with arsenobenzol compounds has previously been given. Relapses have been recorded even after a course of arsenobenzol and mercury had cleared up all symptoms and rendered the blood sero-negative. In addition to mercury and the arsenobenzol compound, bismuth and iodides are considered to be helpful and effective anti-sypilitic drugs in the treatment of the disease. As patients may show idiosyncrasy to one or the other of these drugs, the course should therefore, be modified without following a scheduled routine treatment blindly.

General treatment. The maintenance of the general health and the increasing of the body resisting powers of the patient are most essential along with the specific treatment of the disease. Living in a hygienic environment, keeping regular hours and taking regular exercises, go a long way to help this specific treatment. Avoidance of overwork and worries and abstinence from alcohol should always be aimed at. Sexual excesses should be avoided. The diet should be variable according to the stage of the disease. It should be plain, nourishing and should contain all the proximate principles of food. During the active stage of the disease a bland non-irritating liquid diet is advisable. The bowels and the skin should be kept freely active. Sulphur water has been utilised in the treatment of syphilis

and is a valuable adjuvant to the treatment. In debilitated anæmic individuals, iron, arsenic and strychnine are effective tonics.

Local treatment. In uncomplicated chancres 33.3 per cent. calomel ointment may be applied or the part may be kept dry by dusting with equal parts of calomel and calamine powder, morning and night. The treatment of a chancre of the lip includes the application of a 10 per cent. calomel ointment or 15 per cent. ammoniated mercury ointment. Before the application of the ointment or the powder the part should be bathed with some antiseptic lotion such as eusol, weak biniodide of mercury (1 in 10,000), or weak carbolic lotion (1 in 80). When a chancre is attended with considerable amount of sepsis the condition should be treated on ordinary surgical lines with good drainage, hot fomentations applied twice daily and canterising the focus with pure carbolic acid or acid nitrate of mercury. In sub-preputial chancre with much retention of septic discharges an operation of dorsal slitting of the foreskin or circumcision may be necessary. Gargles with chlorate of potash, alum sulphate, borax or a weak solution of peroxide of hydrogen, are of much value where the mucous membrane of the mouth is involved. Condylomata should be dusted with a powder containing equal parts of calomel and calamine and the surrounding parts should be kept scrupulously clean. In lesions of the skin, specially in pustular conditions such as rupia, hot antiseptic baths containing sanitas or potassium permanganate are effective therapeutic measures in cleansing the parts. The local treatment of ulcerated gummatous conditions in the tertiary stage of the disease consists in cleansing the parts with mild antiseptic lotion and applying hot fomentations afterwards.

Specific treatment. Syphilis is one of the few infectious diseases for which specifics are known; and in this instance there are four; mercury, bismuth, arsenic, and potassium iodide. (For the therapy of these drugs, see pages 736, 708 and 653).

The health organisation of the League of Nations published lately the results of an inquiry into syphilis treatment carried out in five countries (Denmark, France, Germany, Great Britain, United States of America); 98 clinics in these countries have contributed to the inquiry and 13,198 case records of primary and secondary syphilis have been analysed.

Guided by the principles revealed by the study of these records, the experts who have collaborated have adopted the following recommendations which are of great interest to syphilologists, public health officers, and private practitioners :—

1. Treatment should be recommended as early as possible in the sero-negative primary stage. In this connection, the fullest possible use should be made, for purposes of diagnosis, of the microscopical

examinations of the secretion from primary lesions or from lymph glands.

2. It should be emphasised that, prior to the institution of either of the systems of treatment outlined below, there should be an adequate physical examination to determine the absence or otherwise of any indication for caution in respect of the dosage.

3. It is essential that, in carrying out the treatment, a strict supervision of the patient be exercised, especially in respect of mucous membranes, skin, kidneys and liver.

4. Observation, clinical and serological, after completion of treatment should be adequate and in any case for not less than three years.

5. Adequate examination of the spinal fluid, at least before dismissal from observation, is essential.

6. The principles to be followed in carrying out the actual treatment should be as follows :—

(a) To employ a comparatively heavy individual dosage of the arsenobenzene and of the bismuth or mercurial compounds, the doses being administered in comparatively rapid succession, especially at the commencement.

(b) To maintain persistent attack on the disease, avoiding intervals of such length as to afford the parasite an opportunity of recovery.

(c) To administer approximately as much treatment to primary as to secondary cases.

7. The material studied does not enable clear decision to be made as to the relative merits of intermittent treatment with courses of injections in rapid succession separated by rest intervals of some weeks, and continuous treatment, or between the simultaneous employment of both arsenical and bismuth or mercury and the system in which bismuth and mercury are withheld until a number of arsenical injections have been administered.

Nevertheless it seems practical from the results of the analysis and from the personal experience of the experts to formulate a system of intermittent treatment and one of continuous treatment either of which can be expected to yield satisfactory results in ordinary cases of early syphilis.

It seems possible that the intermittent treatment which is suggested below may in effect be continuous or practically continuous, owing to the continued absorption of bismuth from the sites of the injections for some weeks after any temporary suspension of the treatment.

1. *Males*: For adult males of average weight aged less than 50 years and in whom there is no contraindication, a number of courses of injections is given on the plan described below. It should be said that, at the beginning of this course, some administer at once the full weekly dose (0.60 to 0.75 gm.), while others divide it into two doses (*e.g.*, 0.30 and 0.45 gm.) so far as the first week is concerned.

Weeks.		'914' (gramme)	'606' (gramme)	Insoluble compound of bismuth containing bi-metal; (gramme)
1st to 8th	...	0.60 to 0.75	0.4 to 0.5	and 0.20 to 0.24
9th	0.20 to 0.24
10th	0.20 to 0.24

By insoluble bismuth is here meant compounds of a very slight solubility in water. They should therefore be 'given in suspension, those of extremely slight solubility (the oxychloride, etc.) usually in a watery suspension, those that are more soluble (the subsalicylate, the iodobismuthate of quinine, the alkaline tartrates, etc.) suspended in a vegetable oil. If a *liposoluble* compound (e.g., the camphocarboxylate, etc.) is preferred, it is desirable that the injection be given twice weekly in half doses.

The dosage of all bismuth compounds should be calculated according to their content in bismuth metal.

As an alternative to bismuth, a course of mercury may be given, either in the form of inunctions (40 days at 3 gm. of unguentum hydrargyri) or 70 mg. calomel or 120 mg. salicylate of mercury, etc., suspended in a suitable base.)

It is recommended that: (a) in cases which remain or become serologically negative, during or by the end of the first course, four such courses be administered, with intervals of three to five weeks between any two courses.

(b) In cases which have not become sero-negative by the end of the first course, in addition to the amount of treatment shown in (a), further courses should be administered until the patient has received as a minimum three beyond that which has ended with negative serum reactions. At the option of the individual clinician, this treatment may be prolonged as may be considered necessary.

(c) Cases presenting signs of clinical relapse of an early type should be dealt with on principles similar to those enunciated in (b).

2. *Females*: For females (non-pregnant), treatment should be administered on the plan outlined for men with the exception that the single dose of '914' should be reduced by 0.15 gm. and that of '606' by 0.1 gm.

In the event of any reduction in the amount of treatment being indicated it is recommended that this be effected by reducing the number of arsenical injections rather than by reducing the individual dose or increasing the intervals.

As an optional scheme more in harmony with the trend towards longer courses, three series of ten to twelve injections each of arsenical drugs may be given. To secure an overlapping of the heavy metal and the arsenical, believed by some observers to protect against neuro-relapses, begin the bismuth, two, three, or even four injections before the end of the longer arsenical course, continue it through the period

in which the arsenical is suspended, and on into the beginning of the next arsenical course. The bismuth is then suspended while the arsenical course is completed.

The following is the plan of alternating continuous treatment for early syphilis (League of Nations) :—

	'606' (gramme)	Intermittent treatment.	Serol test.	Remarks.
Day		*		
1	0.3 to 0.6		1	'606' dosage for first 3 injections at level of 0.1 gm. for each 25 lb. (11.3 kg.) body-weight. Average subsequent dosage, 0.4 gm., men ; 0.3 gm., women, the fourth and subsequent injections in the first course at weekly intervals. In average patient, all lesions heal rapidly and blood serological reaction becomes negative during first course. If '606' cannot be used, substitute 8 to 10 doses 0.3 gm. silver arsphenamine (silver salvarsan), silver arsenobenzol, etc., or 10 to 12 doses '914' (0.45 to 0.6 gm. maximum for women and 0.6 to 0.75 gm. for men). This applies also to subsequent courses.
5	0.3 to 0.6			
10	0.3 to 0.6			
Week				
3	0.4			If mercury is used ; note overlap (bismuth and arsenic) of week at end of first and start of second '606' courses.
4	0.4			
5	0.4			
6	0.4			
7	0.4			'606' starts, bismuth stops. Watch for provocative serologic reaction after first dose of '606'. Try to prevent short lapses in treatment, especially at this early stage.
8		Bismuth 4 doses, 0.2 gm. and potassium iodide, or unguentum mercury and potassium iodide.	1	
9				
10				
11				Bismuth is better than mercury. Use if possible. Examine cerebrospinal fluid if patients' co-operation can be secured at about this time. If found to be abnormal, continue or intensify treatment as required, re-examining fluid within six months.
12	0.4		1	
13	0.4		1	
14	0.4			
15	0.4			
16	0.4			
17	0.4		1	
18-23		Bismuth 6 doses or unguentum mercury and potassium iodide.		

'606' (gramme)	Intermittent treatment.	Serol. test.	Remarks.
24 0.4			
25 0.4			
26 0.4			
27 0.4			
28 0.4			
29 0.4			
30-37	Bismuth 8 doses or unguentum mercury and potassium io- dide.		
38 0.4		1	
39 0.4			
40 0.4			
41 0.4			
42 0.4			
43 0.4		1	
44-53	Bismuth 10 doses or unguentum mercury and potassium io- dide.		Note that bismuth or mercury courses are gradually get- ting longer—4, 6, 8, and now 10 weeks.
54 0.4		1	The average sero-negative, sero-positive primary or early secondary patient should have at least 5 courses of '606'.
55 0.4			
56 0.4			
57 0.4			
58 0.4			
59 0.4		1	
60-69	Bismuth 10 doses or unguentum mercury and potassium io- dide.		It is safer to finish treatment with bismuth or mercury rather than with '606'.
70-122 proba- tion.	No treatment.	6-11	

123 complete physical and neurological examination, lumbar puncture, and if possible, fluoroscopic examination of heart and great vessels.

The bismuth salt advised for this system is bismuth salicylate in oil suspension, in full adult dosage with due regard for weight. Other preparations of bismuth may be used only with due regard for an equivalent metallic content and for their rate of elimination. The mercurial inunction is 50 per cent. metallic mercury in a suitable fatty

base, dose 4 gm. per inunction, five to six inunctions per week. The use of iodide is optional, depending on indications. The use of insoluble mercurials intramuscularly in this system is not recommended.

It should be further understood that when heavy metal is employed after the last '606' course, the heavy metal courses are to be separated by rest intervals of six to eight weeks between each series of ten weeks injections, or each course of 40 inunctions.

In case of primary syphilis which has remained sero-negative throughout, a minimum of five courses of '606' or '914' should be given. Cases of sero-positive primary syphilis should receive the full treatment called for by this system. In cardiovascular and visceral syphilis small doses are preferable and either arsenic or bismuth should serve the purpose best combined with the administration of iodides. The treatment thus suggested should never be rigidly followed but should be modified according to the reaction of the patient and the diseased tissues. The after treatment of the late cases should be on similar lines as that of persistent sero-positive syphilis. It is better to saturate the patient with the drugs over a prolonged period than to overtreat him with intense therapy for a short period. The treatment should continue for a minimum period of two years and the patient should be under observation for four years during which the blood and the cerebrospinal fluid should be examined from time to time. Short courses of oral medication with mercury and iodide during the course are of definite benefit in these cases.

Neurosyphilis. The treatment of neurosyphilis presents difficulties which are not met with in other systemic cases. No therapeutic agent is as yet known capable of regenerating damaged nerve tissues and even the common anti-syphilitic remedies can hardly penetrate the diseased tissues to effect a cure. In these cases, vigorous and prolonged therapy with antisyphilitic drugs is indicated. The administration of iodides should be encouraged during and subsequent to the treatment with arsenic and bismuth. During a course of treatment for 2 months Lees recommends intravenous administration of '914' in doses of 0.3 gm. at weekly intervals for 3 doses and intramuscular injection of sulpharsenol commencing with doses of 0.15 gm. to 0.6 gm. at weekly intervals for 9 doses. Combined with the arsenic therapy about 9 doses of bismuth are given at weekly intervals commencing at doses of 0.4 gm. and rising to 0.5 gm. After the treatment the patient should rest for a month and then a subsequent treatment should be modified according to the clinical signs and symptoms and the effect of treatment on the blood and the cerebro-spinal fluid. Dercum holds that by draining off the cerebrospinal fluid and thereby lessening the intrathecal pressure; the passage of substances from the systemic circulation to the choroid plexus is facilitated. In this method, within two hours of an intravenous administration of '914', spinal drainage is undertaken and such drainage is carried out once weekly throughout a course of 7 to 9

injections. Shift and Ellis advocated a combined intravenous and intraspinal therapy in neurosyphilis with a view to obtaining a maximum therapeutic effect on the diseased parts. About 40 c.cm. of blood are withdrawn from a patient an hour subsequent to the intravenous administration of '914'. The blood is allowed to clot, the serum is centrifuged and ultimately removed. About 10 c.cm. of this serum are diluted with 18 c.cm. of normal saline and the whole is inactivated by heating to 50°C. for half an hour. A quantity of the spinal fluid is withdrawn by a lumbar puncture and the prepared salvarsanised serum is allowed to flow slowly into the spinal canal by gravity. The foot of the patient's bed is kept elevated for one to two hours afterwards. The injection of salvarsanised serum may be repeated at intervals of two or three weeks and a course consists of seven to nine such injections. Purves-Stewart advocates the introduction of salvarsanised serum or other anti-syphilitic drugs by the cisternal route. It is suggested to be a more efficient method than the intraspinal one though the technique is rather difficult. Tryparsamide is highly reputed in all early cases of meningo-vascular syphilis, in early cases of general paralysis of the insane and in hemiplegias, it is considered to be a most potent drug in controlling the serological changes and rapidly improving the clinical condition of the patient in neurosyphilis. Though the drug is not a strong spirochaetocidal agent it has a high degree of penetration and a powerful stimulative effect on animal economy and animal resistance. The dose of tryparsamide should not exceed 3 gm. weekly for average patient and it should not be repeated more frequently than once a week. The routine course consists of eight intravenous injections given weekly, the first dose is 1 gm., the second of 2 gm. and the remaining of 3 gm. each; along with it, eight weekly intramuscular injections of bismuth or mercury are also given. As many as twelve courses spread over a period of 3 to 4 years may have to be given in resistant cases. The only contra-indication of the drug is diseases affecting the optic nerve. Besides the treatment with drugs other forms of therapy have also given encouraging results.

Protein shock therapy. It has been observed that considerable improvement or even cure is effected by artificial inducement of fever or leucocytosis by inoculation with bacterial or saprophytic organisms, milk or various other chemicals. Typhoid vaccine, *Bact. coli* vaccine, milk, etc., have been used for this purpose. Sulphur has also been injected intramuscularly to produce fever and this has produced beneficial effects in neurosyphilis. The preparations in common use are sulfosin and consul. The latter is given intramuscularly in doses varying from 1 to 5 c.cm., but the malarial treatment seems to be far more effective than the treatment with sulphur.

Malaria therapy. This treatment started from the observations that were made for over a century that intercurrent infections, such as artificially produced abscesses or fever have a beneficial effect on

the symptoms of general paralysis of the insane. Now-a-days malarial therapy is being largely practised in the treatment of neurosyphilis. The syphilitic patient chosen for this treatment, should be fairly healthy where the treatment can be carried out without danger and the attack can be controlled by antimalarial drugs. About 2 to 4 c.cm. of blood are taken from the vein of a patient suffering from an attack of benign tertian malaria. The blood is injected subcutaneously between the scapulæ on the back of a syphilitic patient. After an incubation period of one or two weeks the patient develops an attack of malaria. The patient is allowed to have eight to twelve pyrexial attacks before quinine is administered to control them. In a few cases the patient may not react to malaria. To control the pyrexial attacks after eight to twelve of them have occurred quinine is administered. When the malarial treatment is finished a patient improves in health and puts on weight. Once a syphilitic patient has been inoculated with benign tertian malaria, his blood can be used as a stock, and from him blood can be transmitted to other syphilitics. This transmission from patient to patient does not make the treatment less effective. It is suggested that in neurosyphilis, especially in advanced cases of general paralysis of the insane, the malarial therapy followed by tryparsamide is most beneficial in many cases.

Congenital syphilis. The treatment should be continued for 3 years. In the first year, if the baby has cutaneous lesions a perchloride of mercury bath, 20 gr. in 2 gallons of warm water, is recommended; 10 to 20 gr. of mercury ointment or unguentum cinereum is rubbed gently for half an hour every other day. After that, mercury in form of grey powder, $\frac{1}{2}$ gr. three times daily in milk, should be given internally for two months. Colloidal iodine, $\frac{1}{2}$ to 1 dr. twice daily, should then be prescribed for one month. In the second and third year, mercury is given internally for 3 months, colloidal iodine for 1 month with a period of rest for 1 month, subsequently mercury is given for 4 months, iodine for 1 month, with a rest for 2 months. Children over 7 years of age may be treated with proportionate dosage of arsenobenzol, bismuth or mercury. The average commencing dose of an arsenic preparation during the first year of life is from 0.025 to 0.05 gm., each week. The dose is much less in debilitated marasmic children and is generally 0.0075 gm. or even less. During the second year of life, the dose may be increased from 0.05 to 0.075 gm. of '914' in cases of healthy children. Bismuth is generally given biweekly in doses varying from 0.025 to 0.05 gm. Mercury may be given instead in doses commencing from 1/20 gr. each week.

Pregnancy complicated with syphilis. The antisymphilitic treatment is well borne by the syphilitic mother. An increased strain is generally put on the excretory organs during the course of treatment and the urine should be carefully watched from time to time to detect traces of albumin. Many pregnant women do not tolerate iodides and treatment should

therefore include the administration of '914', bismuth and mercury. The whole course of treatment generally covers a period of six months, divided into periods of three months. During the first three months, 4 doses of '914' each of 0.45 gm. are given at weekly intervals and then after a period of rest for a month, another 5 such doses are given at weekly intervals. Four doses of bismuth, each 0.4 gm. are given at weekly intervals during the period of rest from the arsenic. In the next three months of treatment, 8 doses of bismuth each 0.4 gm., are given at weekly intervals with a period of rest for a month in between the injections during which 4 doses of '914' each 0.45 gm. are given during the intervals. In every case treatment should be modified according to the tolerance of the patient. The dosage and the time intervals of administration of different drugs should be accordingly modified. In all cases it is necessary to continue the treatment after the puerperium on the same lines as for the routine treatment in systemic cases. It is suggested that the patient should receive courses of antisyphilitic treatment in her subsequent pregnancies even though clinical examinations give negative results.

Prophylaxis. The prophylactic treatment resolves itself into the two factors, namely, the reduction of the number of infection-carriers and the prompt disinfection of those who have been exposed to risk of contagion. All persons after exposure should submit to abortive treatment. The disease can be successfully treated if seen early and cures can be guaranteed in those cases. Infection carriers generally result from failure to cure. Women are more liable to be infected than men. Disinfection of the exposed parts carried out in an efficient manner often succeeds if performed within four hours of exposure. The general line of treatment laid down is that the genitals, pubis, and lower abdomen should be well washed with soap and water. The part should be dried and swabbed well with perchloride of mercury lotion (1 in 2000) and particular attention should be paid to the mouth of the prepuce, corona, and frenum, all of which are liable to be abraded during intercourse. An application of 33 per cent. calomel ointment in lanolin is considered to be highly beneficial in disinfecting the parts. Stovarsol tablets each 4 gr., 4 such every morning before breakfast for 4 days and repeated in the second and third week after exposure to infection are also of value. Apart from these drugs protection is also afforded by the careful use of a condom or sheath during intercourse.

SYSTEMIC DISEASES, ORAL MANIFESTATIONS OF. The oral cavity serves as an index of generalised infection of the body. The altered character of the oral mucosa from the normal pink colour to a general pallor is strongly suggestive of anaemia. Similarly, a purplish colouration of the mucous membranes, particularly of the lips and tongue strongly suggests an insufficient oxidation of blood haemoglobin (anoxaemia) in serious chronic diseases of the heart and lungs. Dryness of the mucous membranes is an indication of a depletion of body

fluids or dehydration, seen in severe untreated diabetes, uræmia, prolonged vomiting from various causes and also in persons with nasal obstruction who are popularly known as mouth-breathers. Brownish pigmentation of the oral mucosa is seen in Addison's disease. Ulcerations, exudations and deposits on the gums, tongue and elsewhere often appear as local manifestations of general infections, toxæmias, chemical poisoning, dietary deficiencies or serious diseases of the hæmopoietic organs.

A coated tongue is seen in fevers and in gastro-intestinal disorders, especially associated with gastric hyperacidity. Gastric hyperacidity tends to smooth the tongue with atrophy of the papillæ. A disturbance in motility or sensation is usually associated with disorders of the nervous system, organic or functional (hemiplegia and hysteria) and certain malignant growths involving the organ.

Syphilis, tuberculosis and actinomycosis produce ulcers with marked induration. In syphilis, both the primary and secondary manifestations are seen in the mouth. The papillæ of the tongue become more prominent and an exudate is usually found in the faucial tonsils in follicular tonsilitis, scarlet fever, etc. In Vincent's angina, a punched out ulcer with a dirty exudate around the tonsil is seen with tender and painful lymph nodes below the angle of the jaw.

Many diseases of the skin also affect the oral mucosa and among these are lichen planus, lupus erythematosus, erythema multiforme, pemphigus and angioneurotic oedema. Papules of the buccal mucosa with circular or conglomerate patches on the tongue or lips suggest lichen planus. Lupus erythematosus appears as greyish or reddish spots or patches which may ulcerate. Pemphigus of obscure origin, occurs as blebs and ulcers on the mucous membranes and resists all treatment with a tendency to frequent recurrences. In measles, Koplik's spots usually appear first in the mouth as small bluish-white spots, each on a red base later becoming whitish and numerous.

The salicylates and their derivatives, barbituric acid compounds, phenolphthalein, potassium iodide all produce rashes involving the mucous membrane of the mouth. Benzol, bismuth, lead and mercury cause characteristic intraoral changes. Lead produces a bluish deposit on the gums. Bismuth and mercury produce severe stomatitis with violet or black pigmentation and later ulceration.

Intraoral changes are chiefly associated with endocrine dysfunctions such as hypothyroidism and Addison's disease. In the former, the tongue is thickened and in the latter, pigmented areas are seen on the oral mucosa.

In deficiency diseases marked changes are met with in the oral cavity. In scurvy, the gums become hypertrophied and soft, and often bleed considerably; a sore tongue with atrophy of papillæ and redness is characteristic of pellagra; swelling and multiple superficial ulcerations appear later, simulating those of pernicious anæmia.

Pernicious anaemia shows pallor of mucous membranes of the oral cavity and tongue. In tropical sprue, the tendency to ulceration and atrophy of the tongue is more marked. Polycythæmia is evidenced by cyanosis of the lips and tongue. Bleeding and swollen gums resembling scurvy are seen in purpura. A general anaemia of the oral mucosa and hæmorrhage from the gums appear as early signs in fatal leukaemias.

TETANUS. Tetanus or lockjaw is a specific disease caused by the toxins of the tetanus bacillus, an anaerobic organism. The bacilli occur in the intestines of animals, such as the horse and cow. Man is infected through a wound contaminated with soil containing the spores. The bacilli remain localised, but give rise to exotoxins. These are absorbed from the end plates of motor nerves and pass up through the perineural lymphatics. The incubation period is about 12 days, but may be as short as 2 days or prolonged to several months.

Diagnosis. (1) History of wound. (2) Clinically, trismus, stiffness, opisthotonus, spasms, etc., are characteristic in a typical case. The mind remains clear and the patient is in great agony. It is easily differentiated from strychnine poisoning in which the jaw and neck are not affected, there is complete relaxation between spasms and the body temperature is normal. (3) Moderate leucocytosis. (4) Cerebrospinal fluid comes out under pressure.

TREATMENT. (1) The patient is kept in a dark and quiet place. (2) Antitetanic serum is given early, desensitising the patient if necessary (see also serum therapy, page 791). An intravenous injection of 20,000 units diluted with an equal volume of warm normal saline is given slowly. A lumbar puncture is then made under general anaesthesia and 20,000 units of concentrated serum is given intrathecally. These intravenous and intrathecal injections are repeated during the next two days; on the 4th day 10,000 units are given intramuscularly and repeated if necessary. (3) Chlorotone 40 gr., olive oil 1 oz., may be given per rectum. Chloral hydrate 15 gr. and potassium bromide 20 gr. given 4 hourly by mouth when the patient can swallow. (4) Chloroform is administered if spasms are severe. (5) One c.cm. of 25 per cent. solution of magnesium sulphate per 25 lb. body weight given intrathecally sometimes produces good results. (6) Rectal saline and glucose.

Prophylaxis. Serum in doses of 500 units subcutaneously or intramuscularly repeated three times at weekly intervals.

Curare treatment. The chief effect of curare is to paralyse the voluntary movement by blocking the passage of impulses from the peripheral nerves to the muscles. Along with the antitoxin treatment and the administration of sedative drugs *per rectum* such as paraldehyde, avertin, etc., dose of 32 mgm. of the drug for adults is injected subcutaneously and is generally repeated at six hourly intervals. In severe cases, four such doses would bring about an improvement in the condition clinically, but repetition of treatment might be necessary on recurrence

of symptoms. No unpleasant symptoms or serious after-effects follow these injections. Observations on the effects of curare treatment in tetanus are hopeful but dosage at present is a difficult problem and will remain so until a standardised preparation of the drug is available.

TRYPANOSOMIASIS. African sleeping sickness. It is a disease endemic in tropical Africa and is characterised by pyrexia with enlargement of lymphatic glands, followed by nervous changes and increasing torpor. It is produced by infection with a trypanosome, which is a flagellate protozoon. Man is infected by the bite of the tsetse fly. There are two main types:—*T. gambiense* and *T. rhodesiense* occurring in different parts of Africa.

Diagnosis (1) Clinically there is irregular pyrexia and enlargement of superficial glands (especially the cervical) in the early stage, due to invasion of the blood and lymphatic glands. There may be splenic enlargement, oedema of feet and rash on the body. If untreated the disease gradually passes after months or years into the second stage of drowsiness. In the third stage the patient is bed-ridden and comatose. (2) Blood. (a) Trypanosomes in the centrifuged deposit. (b) Excess of globulin in the serum. (c) Secondary anaemia. (d) Aldehyde test may be positive. (3) Gland puncture shows trypanosomes. (4) Guinea-pig inoculation. (5) Cerebrospinal fluid in the second stage shows: (a) excess of cells (50 or more per c.mm.), (b) excess of protein and (c) presence of trypanosomes.

TREATMENT. (1) Atoxyl 3 to 7 gr. in 10 per cent. solution are given intramuscularly once a week for a month and then at monthly intervals till all signs disappear; test vision from time to time. (2) Soamin may be used similarly. (3) Tryparsamide, another arsenical preparation is especially useful for advanced cases. It is given intravenously or intramuscularly in doses of 1 to 3 gm. in 10 c.cm. of water every week, until a total of 20 to 100 gm. has been given according to the severity of the case; the average dose is 0.04 gm. per kilo. of body weight. Visual disturbances are a signal for stopping injections, but they are only temporary. Good results are also sometimes obtained by intravenous injection of tartar emetic and this drug was largely used in former days; it has now been superseded by a new organic preparation. (4) Germanin or Bayer '205', is administered by intravenous injection in doses of 15 gr. in a 10 per cent. aqueous solution weekly till 45 to 60 gr. have been given. This is particularly useful in early cases, but in later stages tryparsamide is best.

Prophylaxis. Injections of germanin before going into a fly area afford protection. Patients must be isolated and measures taken to destroy the tsetse flies. (See also page 466).

SOUTH AMERICAN TRYPANOSOMIASIS. It is a form of human trypanosomiasis met with in south America caused by *Trypanosoma cruzi* and disseminated by certain bugs. It is characterised by acute fever

with adenitis and involvement of the spleen, thyroid, nervous system and heart muscle. Unfortunately treatment is not very effective in this condition

TUBERCULOSIS. See page 945.

TYPHOID FEVER. See page 830.

ULCER. An ulcer is a defect of the body surface due to loss of epidermal covering. It may or may not be the outcome of an infective process, its shape and size may vary, it may or may not be painful, and may be acute indolent or indurated. In acute infective processes it tends to spread. This is seen in chancroids, syphilomas, tuberculomas, malignant growths, because of malnutrition of the tissues. The specific ulcers need different treatment.

Disinfection is rather difficult in infective ulcers because no antiseptic is yet known which will destroy the bacterial cells only without killing the tissue cells at the same time. The use of strong antiseptics, adds injury to the devitalised tissues suffering from deficiency of nutrition as in cases of thrombosed or varicose ulcers. In all infective ulcers drainage should be the chief measure for removing infection without damage to the tissues. Drainage is indicated in profusely secreting ulcers with signs of acute inflammation. Hydrogen peroxide along with hot boric acid lotion may be used as a cleansing agent and this may be changed every two hours during the day and if possible every four hours during the night until healthy granulating tissue has developed and the infiltration of the edges of the ulcers has disappeared. A hot 10 per cent. magnesium sulphate solution compress is held to be superior to the boric acid dressing as the hypertonic solution, by inducing exosmotic currents, cleanses the ulcers and relieves the pain of the patient. A constant bath in a warm (95° to 100°F.) dilute solution of potassium permanganate is a valuable means of rendering it inoffensive if the ulcer is foul-smelling. When the odour is overcome, hot boric dressings may be used. Moist dressings are beneficial in ulcers surrounded by dermatitis. Eczematous ulcers require uncovered compresses. For moistening these a solution of aluminium subacetate (diluted 1 in 10) is a most useful primary dressing to be followed as soon as the ulcer appears clean. Adherent dressings often delay healing by injuring the healthy granulating tissues, hence moist dressings are preferable and require renewal at intervals of not more than 3 to 4 hours. Some protection against physical injury and infection should always be aimed at after an ulcer is fairly clean and healthy. Wire-gauze screens protect ulcers and promote healing by exposing them to dry air and sunlight. The screen should be nicely shaped so as to fit the wound. Absorbent dressings, as they act like a foreign body when in contact with the ulcers, should be discarded. It generally keeps the skin edges waterlogged and the epithelium does not grow well over the ulcerated surface. For epithelization to be complete and satisfactory, the clean wound should be covered with a dry

adherent scab which will be spontaneously detached after healing is complete. Surgical paraffin (melting point $50^{\circ}\text{C}.$) is preferred by many for dressing these ulcers. The paraffin film by providing a more physiologic condition for healing aids the growth of epithelium over the wounded surface. Being perfectly bland, the paraffin does not kill cells as do most antiseptic dressings and moreover the living cells are not injured when this paraffin is removed from the ulcer. The raw surface is at first painted with sterile liquid petrolatum before the application of the paraffin ; over this a thin layer of sterile cotton is applied and next the melted paraffin is laid over it by a series of gentle pats. The paraffin should completely seal the wound. A second film of paraffin may be painted over the first one. The dressings might require changing at intervals of 24 to 48 hours or even longer. A mixture of paraffin, one part and petrolatum two parts may be used but it is less efficient because it does not retain the wound secretions. In painful ulcers a 10 per cent. ethylamino-benzoate (anesthesine) may be incorporated with advantage. In ulcers resulting after deep burns such as from electric currents, silver foil has been advocated as a suitable dressing. It clings closely to the surface, is bacteriostatic and helps in the accumulation of wound secretion which serves as a culture medium for the proliferating cells. In this treatment keloid formation seems to be less marked than in others. Indolent ulcers require a stimulative treatment for rapid healing by increasing the blood supply and stimulating the proliferation of cells. The application of irritant drugs is indicated only when the ulcer-bed is well filled and their use should be discarded as soon as exuberant granulation tissues develop. Radiant energy is most beneficial in extensive ulcers, particularly associated with poor blood supply. This can be achieved with direct exposure to the heat of the electric cradle or continuous exposure to ultraviolet rays of the sun. The latter rays are considered to have a considerable amount of antiseptic value while excessive exposure should always be avoided lest it might produce necrosis of the tissues. Balsam of Peru is particularly valuable in the treatment of bed sores. It is not only a good stimulant to healing but is also bacteriostatic and keeps dressings from sticking. It may be used in the form of a paste with zinc oxide or mixed with castor oil in equal parts. A useful prescription of Balsam of Peru paste includes balsam of Peru 10 gm., zinc oxide 40 gm., castor oil 50 c.cm. Compound tincture of benzoin forms a varnish after evaporation of the alcohol which is protective and such treatment is particularly suitable for small indolent sores.

In certain intractable ulcers periarterial sympathectomy becomes necessary for prompt healing. The growth of epidermis should be stimulated for the proper healing of an ulcer and reducing agents have a special reputation for this purpose. Of drugs similarly reputed a 5 per cent. scarlet red ointment applied to the growing epithelial margin for a couple of days deserves mention. Gauze impregnated with compound scarlet red ointment containing oxyquinoline sulphate 0.6 gm.

chlorbutanol 2.4 gm., liquid paraffin 4 c.cm. and 5 per cent. scarlet red ointment 120 gm., is specially recommended by Bettman (1931) for preparing ulcers for skin grafting later on. Thiocresol compresses advocated by Reimann (1930) are of proved value in extensive ulcers. Thiocresol should be freshly prepared in a 1 in 10,000 dilution. A stock solution of thiocresol contains thiocresol 0.1 gm., alcohol 50 c.cm., 5 c.cm. of this should be mixed with 100 c.cm. of distilled water to make 1 in 10,000 dilution. The solution is poured on sterile gauze and placed directly over the wound. This dressing is best alternated after forty-eight hours with simple dressing such as compresses of physiologic solution of sodium chloride. The most important conditions retarding healing are exuberant granulation, a callous ulcer margin and ulcer completely encircling a limb. Exuberant granulations may be destroyed by curetting or sometimes require trimming with scissors. Cauterization with silver nitrate applied once or twice a week very often restrains such growth. The visible epithelial margin should never be touched with caustics. This procedure generally retards healing for some time. Cauterization with stimulating astringents like copper sulphate or zinc chloride is preferable to silver nitrate in cases of anæmic ulcers with pale flabby granulations. This should be followed by dry treatment such as dusting with thymol iodide and a compression bandage. A firm strapping with elastic adhesive plaster serves the purpose very well. Treatment of callous ulcers presents difficulties. Hydrotherapy in the form of hot circular compresses may produce a macerating effect on the tissues and increase the blood supply to the part and thus expedite healing. Local hypodermoclysis with physiologic solution of sodium chloride may assist this softening effect by its lymphagogue action. Along with the hot compresses preferably during the night alternated with a pressure bandage during the day is of advantage. Irradiation treatment with Roentgen rays in fractional doses, an occasional erythema dose of ultraviolet rays, or daily graduated doses of the sun rays deserve a trial.

When the above treatment fails surgery should be adopted as a last resort. Incisions are to be made through the indurated margin, radiating from the centre of the ulcer, penetrating the deep fascia and extending for one or two inches beyond the margins of the ulcer. After complete excision of the ulcer and as soon as healthy granulation tissues have developed, skin grafting should be undertaken for the rapid healing of the wound. Sometimes amputation is required when an extensive ulcer encircles a limb and when plastic operations fail.

Varicose ulcer has been treated with the topical application of 5 per cent. gentian violet. After thorough washing and subsequent drying of the ulcer, a 5 per cent. aqueous gentian violet solution is sprayed on with an atomizer or is sometimes directly applied over the ulcer. A dry sterile dressing is then employed after the gentian violet has dried. This treatment is repeated every other day until a firm

crust has formed and finally complete healing occurs. Varicose ulcers have also been successfully treated with warm saline dressing Unna's paste, Dakin's solution, ultraviolet light, scarlet red ointment and 70 per cent. alcohol.

Bed sores. Factors which usually predispose to development of bed sores are prolonged pressure, maceration and trauma to the part. Prolonged pressure especially over the bony prominences such as the sacrum, shoulder blades, heels, ankles and elbows, should be avoided or minimised by a water bed or a cushion filled with water at 95°F. To improve circulation in the tissues of the back, massage is beneficial and some recommend 50 per cent. alcohol for rubbing. The direction of massage should be from the base of the skull downwards and afterwards the patient's skin should be dusted with talcum powder or zinc stearate. When the skin is dry and rough, an ointment consisting of zinc stearate 5 gm., tincture of benzoin 5 gm., 5 per cent. scarlet red ointment 0.25 gm., hydrous wool fat 30 gm., liniment of camphor 180 c.cm. and mutton tallow 500 gm. may be used. Daily cleansing the sores with alcohol kills the cells. The ulcers require stimulation for which balsam of Peru serves the purpose best. It should be mixed with castor oil to prevent the burning sensation, especially when it is applied to sensitive ulcers. A 5 per cent. scarlet red ointment is an ideal stimulant for the growth of epithelium. Thiocresol compresses have of late been advocated to stimulate healing of extensive ulcers. A freshly prepared 1 in 10,000 solution of the 2 per cent. alcoholic solution, 5 c.cm. is mixed with 100 c.cm. of distilled water and is applied on the gauze which is then covered with waterproof material. This dressing is changed every two hours. To avoid excessive irritation, it should be alternated with compresses of physiologic solution of sodium chloride at intervals of forty-eight hours.

Absorbent materials should be used to prevent damage to the skin due to constant wetting with sweat, urine, faeces, etc. All forms of trauma should be avoided, as trauma, however slight, permits invasion of bacteria. In threatened bed sores with signs of cutaneous erythema, the skin should be hardened with a 5 per cent. solution of silver nitrate in distilled water. The following solution is useful for painting when there are small breaks in the skin: alum 30 gm., water and alcohol each to be added 250 c.cm. For unavoidable bed sores a useful preparation is a 5 per cent. aqueous solution of tannic acid sprayed on the uncovered area of the skin and later on dried by a current of warm air. Moist treatment is only indicated in cases of spreading infections and where pus is retained. In these cases warm boric acid compresses and irrigation of the ulcer with a solution of chlorinated soda are most beneficial.

URINE. The examination of the urine may give important information concerning disturbances of metabolism, as well as regarding

diseases of the kidney or urinary passages, and even with regard to functional abnormalities of the liver, or of the heart and circulation.

The examination of the urine should include the following:—

The volume excreted per day, the specific gravity, the colour and the reaction. In addition it should be tested for the presence of albumin and sugar (cloudy urine must be filtered before these tests are made). Urine which contains pus cells or bacteria is usually turbid, and sometimes cannot be cleared by filtration. Under these conditions it must be shaken with kaolin and then filtered. According to its colour the urine should be tested for the presence of bile pigments, blood pigments, urobilin and porphyrin. Finally the urinary sediment should be examined microscopically. In certain cases the examination must include tests for other substances (*e.g.*, in diabetes for acetone and di-acetic acid), and the quantitative estimation of albumin, sugar, nitrogen, etc.

VOLUME. The normal male voids approximately 1500 to 2000 c.cm. per day, and the female 1000 to 1500 c.cm. A daily volume of less than 500, or more than 2000 c.cm. is usually to be regarded as abnormal.

While in the normal individual the urine is excreted principally during the day and only a small quantity at night, it is often observed in patients with heart disease, pyelitis, or vascular disease of the kidneys, that a far larger amount of urine is excreted during the night (nycturia).

SPECIFIC GRAVITY. It is measured by dipping a dry hydrometer into the urine cooled to room temperature. The hydrometer is read at the lower level of the fluid meniscus. The specific gravity is dependent upon the amount and the weight of the dissolved substances.

The specific gravity of the urine ranges normally between wide limits, approximately 1.01 to 1.025. With increased fluid intake large quantities of urine of low specific gravity are excreted, upon a small fluid intake or with a considerable loss of water in the form of perspiration during vigorous exercise, or *via* the bowel in diarrhoea, small quantities of urine are passed having a high specific gravity.

From the specific gravity of the urine the total concentration of solids in grammes may be calculated by multiplying the last two figures of the specific gravity by Haeser's coefficient 2.3. For example, a urine of specific gravity 1.015 contains 34.5 (15×2.3) gm. solids per litre, which, with a total urinary volume of 2,000 c.cm., represents the elimination of 69.0 gm. of solids per day.

COLOUR. The colour of the urine which is normally yellow, is fainter with a dilute urine, and darker and more reddish-yellow, if the urine is more concentrated. Bright yellow urine of high specific gravity is often found with diabetes mellitus. The urine is a dark, yellow-brown (the colour of beer) and has a yellow foam if bilirubin be present, *i.e.*, with icterus; reddish-yellow or reddish-brown if it contains urobilin, a reddish colour with porphyrinuria, a smoky red, *i.e.*

red and at the same time slightly cloudy and iridescent, if blood be present therein. The original normal colour of the urine deepens somewhat upon standing in air and may change to a greenish-brown following the use of phenol, lysol, naphthol, hydroquinine, salol, or with alkaptonuria or melanuria.

REACTION. The reaction of the normal, freshly voided, human urine is acid, principally due to the presence of disodium acid phosphate. Occasionally the reaction of the normal urine may be amphoteric changing blue litmus faintly red, and red faintly blue. This is the case if large quantities of the dibasic phosphates are present together with diacid phosphates. When only the dibasic phosphates, or with these tribasic phosphates are present the reaction is alkaline.

ALBUMIN. Albumin may be demonstrated in the urine by the following tests (turbid urine must be filtered before testing).

1. *Heat and acid.* The urine is heated in a test tube to boiling and one or more drops of dilute acetic acid are then added (instead of dilute acetic, concentrated nitric acid may be used). If a precipitate develops during heating which disappears on addition of the acid, it is composed, not of albumin, but of the phosphates or carbonates of calcium or magnesium which are easily soluble in acid. If there remain even a slight clouding, or if such appears for the first time upon the addition of acid, albumin is present. If the urine is very dilute or poor in salt the addition of a small amount of salt greatly enhances the accuracy of the test. For estimation of the albumin content the Esbach albuminometer may be employed. This method is complicated by the fact that Esbach's reagent (picric acid and citric acid) may sometimes cause a precipitate in normal albumin-free urine, since the picric acid produces an insoluble compound with potassium salts, urates, quinine, urotropin and other substances. As a result the Esbach method may give too high a value following the use of urotropin, or may give a positive reaction in urine that contains no acids. The use of Tsuchiya's reagent avoids this difficulty. 1.5 gm. phosphotungstic acid dissolved in a mixture of 5 c.cm. concentrated HCl and 95 c.cm. of 95 per cent. alcohol.

2. *Heller's test.* Concentrated nitric acid is layered beneath the urine in a test tube by means of a pipette. In the presence of albumin there develops at the boundary between the two fluids a cloudy ring.

3. *Sulpho-salicylic acid test.* If 20 per cent. sulpho-salicylic acid be added to the urine, there develops a definite clouding with small traces of albumin.

ALBUMOSE. Albumoses appear in the urine in many febrile infectious diseases (febrile albumosuria), in some types of poisoning (e.g., phosphorus poisoning), also in the presence of a purulent exudate as in empyema, meningitis (pyogenic albumosuria) in pneumonia, in the puerperium, with ulcerative processes in the intestinal canal. The

proof of the presence of albumoses is of very little diagnostic significance. To test for albumoses it is necessary first to eliminate any albumin which may be present. It can be separated from albumin by saturating the urine with crystals of ammonium sulphate, boiling and filtering. The precipitate on the filter paper is washed with water, when any albumose will be redissolved and carried through the filter paper. The Biuret test is then applied to this filtrate and if positive, indicates the presence of albumoses. With osteosarcoma and other diseases of the bonemarrow (*e.g.*, myeloma) there occurs a type of protein in the urine described by Bence-Jones. To demonstrate this protein the acid urine is heated to about 60°C. At this temperature a precipitate appears, this dissolves again on boiling to reappear as the mixture is again allowed to cool.

SUGAR. 1. *Fehling's test.* For this test two component solutions are prepared: (a) 34.64 gm. crystalline copper sulphate dissolved in water and diluted to 500 c.cm.; (b) 173 gm. of Rochelle salt (potassium sodium tartrate) and 100 c.cm. of pure sodium hydroxide diluted to 500 c.cm. with water. These two solutions are mixed in equal proportions before using. One c.cm. of the mixture should be completely reduced by 0.005 gm. of glucose. Two c.cm. of this mixture are placed in a test tube, diluted with an equal volume of water and boiled. In the absence of contamination no evidence of reduction should appear. One or two c.cm. of urine are added to the tube and the mixture is heated on a water bath. In the presence of glucose there appears a reddish-yellow precipitate of cuprous oxide.

The quantitative determination of the urinary sugar by Fehling's method is carried out as follows: 10 c.cm. of Fehling's solution, 10 c.cm. of concentrated sodium hydroxide and about 50 c.cm. of water are mixed in a basin. The urine is then added gradually from a burette until the blue colour of cupric oxide has completely disappeared. The percentage content of sugar is then calculated from the fact that the volume of urine added must have contained 0.05 gm. of glucose. If the sugar content is known to be high it is sometimes better to dilute the urine to 1 to 10.

2. *Benedict's test.* To about 5 c.cm. of the reagent in a test tube add 8 to 10 drops (no more) of urine, boil the mixture for 2 minutes and allow to cool. Dependent upon the amount of glucose present the mixture turns green, or a green, yellow, or red precipitate appears.

DIACETIC ACID. In the presence of diacetic acid, the urine gives a positive reaction to Gerhardt's ferric chloride test. The urine is mixed in a test tube with several drops of a solution of ferric chloride. This causes the formation (even in normal urine) of a greyish-white precipitate of phosphate of iron. If diacetic acid be present there appears in addition to this precipitate, a burgundy-red colour. Any specimen of urine which contains diacetic acid will always give a positive test for acetone. The reddish brown colour of the urine is

not produced by diacetic acid alone but also by antipyrin and certain other drugs, as well as by amino acids, with this difference, however, that the diacetic acid containing urine also gives a positive test for acetone. Salicylic acid produces a violet colour with ferric chloride.

If the patient has been taking drugs such as aspirin, salicylic acid, or salicylates, etc., misleading results may be obtained. The colour is, however, quite different from that given by diacetic acid, since it is much darker and of a more violet hue. To differentiate this, bring the urine to the boiling point. If the reaction is due to diacetic acid the heat will decompose the diacetic acid and the port wine colour will disappear. If it is due to coal tar drugs the colour will persist.

ACETONE. *Rothera's test.* Take about 2 inches depth of urine in a test tube and saturate it by shaking with finely ground ammonium sulphate crystals. To the solution add a few drops of a recently prepared 10 per cent. sodium nitroprusside solution and about as much ammonium hydrate as the amount of urine taken. The production of a permanganate colour at the junction of the fluids indicates the presence of acetone.

PUS. On adding liquor potassæ, a ropy gelatinous mass indicates pus. (The microscopic test is better).

INDICAN. To some urine add an equal amount of strong hydrochloric acid, then a few drops of hydrogen peroxide. Shake up the mixture with some chloroform. The indican is oxidized to indigo which imparts a blue colour to the chloroform.

BILE SALTS. Hay's test—Sprinkle flowers of sulphur on to the surface of urine in a test tube. If bile salts be present the particles of sulphur sink to the bottom of the tube.

BILE-PIGMENTS. Bilirubin is identified by Gmelin's test. Below the urine in a test tube is layered a small amount of fuming nitric acid. At the interface between the two solutions, in the presence of bilirubin, there is formed a ring of color which changes from green through violet to red and finally yellow. A blue ring may be caused by the presence of indigo, and a reddish-brown ring by urobilin and other substances. Gmelin's test may be carried out in another fashion. If the urine is filtered the greater part of the bile pigments remain upon the filter paper. If upon this yellowish filter paper is placed a small drop of nitric acid the characteristic rings of color form about it. Or several drops of urine may be placed upon an unglazed porcelain plate and touched with a rod dipped in nitric acid.

UROBILIN. It is demonstrated in the urine as follows :—

The urine is mixed with an equal volume of Schelsinger's reagent (zinc acetate 10 gm., alcohol 100 c.cm.) The turbid mixture is then shaken and filtered. In the presence of urobilin the filtrate shows a green fluorescence (best seen by looking down the test tube against a dark background). This test may be rendered more sensitive by mixing 3 drops of a 5 per cent. alcoholic solution of iodine with

10 c.cm. urine to convert all the urobilinogen to urobilin before the addition of the Schlesinger's reagent. Upon spectroscopic examination urobilin containing urine shows a single absorption band between the green and blue, sometimes only after the addition of zinc chloride and ammonia.

Diazo-reaction. *Solution A.* Saturated solution of sulphanilic acid in 5 per cent. HCl solution. *Solution B.* Half per cent. solution of sodium nitrate in distilled water. *Test solution.* Solution A 50 parts, solution B 1 part. To 5 c.cm. of urine add an equal volume of the test solution, shake thoroughly, add a strong solution of ammonia in excess, allowing it to run gently down the tube so as to overlay the mixture below. If the reaction be present a deep red band appears at the junction of the fluids, when shaken it yields a pink or rose coloured foam and after standing several hours, a green precipitate forms. Use fresh urine and see that the reaction is acid and the urine is filtered. Use a freshly prepared test solution.

ORGANIZED URINARY SEDIMENT. Leucocytes appear in small numbers in normal urine. If they are present in abundance the urine is cloudy. This finding indicates an inflammatory or purulent process in one portion of the urogenital tract (gonorrhœa, cystitis, pyelitis, nephritis), the more accurate localization of which often demands further investigation. With jaundice the leucocytes in the urinary sediment sometimes contain fine crystals of bilirubin.

With chronic gonorrhœa the urine contains fine shreds of mucus sometimes mixed with leucocytes, and occasionally intracellular gonococci, even though the original infection has taken place years before. These mucus shreds are discharged from the prostate or posterior urethra. Red blood corpuscles are present in the sediment with the most various hæmorrhagic conditions in the urogenital tract. Cells of renal epithelium are small, round or cuboid with a vesicular nucleus. They are usually poorly developed and often filled with fat droplets. Epithelial cells from the bladder, ureters or renal pelvis are indistinguishable from each other. Those from the superficial layers are flat and polygonal, from the deeper layers round or irregular in contour (pear-shaped) and contain a vesicular nucleus. With an inflammatory process involving the bladder or upper urinary passages large numbers of such epithelial cells, accompanied by leucocytes, are to be found in the sediment. It is, therefore, impossible by microscopic examination alone to ascertain exactly which portion of the upper urinary tract may be diseased. The vagina and prepuce are covered with pavement epithelium similar to that of the mucous membrane. The male urethra is lined with cylindrical epithelium. Gonorrhœal pus sometimes contains such cells but is distinguished particularly by the presence of gonococci.

CASTS. Casts are formed in the renal tubules. They occur in large numbers in acute nephritis and in chronic nephritis with œdema and

less profusely with the contracted kidney and with those forms of albuminuria associated with circulatory failure or fever. With icterus bile-stained casts may be observed. In severe cases of diabetes mellitus large numbers of coarsely granular casts are sometimes found in the urine.

The following types of casts are distinguished. *Hyaline casts* which consist of a homogeneous transparent substance and are often indistinct in outline. *Granular casts* with fine granular matrix, are otherwise similar to hyaline casts. They occur, however, almost exclusively with true renal disease, i.e., with acute or chronic nephritis. *Waxy casts* are refractile, often yellowish, with a distinct contour which is sometimes irregular. They are met with chiefly in chronic renal disease and indicate a more severe degree of renal involvement. *Epithelial casts* are made up of desquamated epithelial cells from the renal tubules. *Red-blood cell casts* represent masses of red blood cells closely packed together. *Cylindroids* are long, irregular masses of mucus and are of no diagnostic significance.

MICRO-ORGANISMS may always be demonstrated in specimens of urine which have stood for any length of time. It is therefore, advisable to search for bacteria only in a freshly voided specimen or still better in one which has been obtained by means of a sterile catheter. With cystitis and pyelitis, bacteria, usually *B. coli communior* are found; more rarely staphylococci, streptococci and pneumococci. In foul-smelling urine *B. proteus vulgaris* is sometimes present, a short variable rod, which liquefies gelatine. In tuberculosis of the urogenital tract tubercle bacilli are to be found in the urinary sediment.

VACCINES. *General rules in the use of curative vaccines.* (1) Accurate diagnosis is essential in regard to the infecting organism or organisms and also in regard to the duration, course, and degree of a disease process. (2) Autogenous vaccines are preferable to stock vaccines. (3) Vaccines too old or too much heated should not be employed as there may be some change in the antigenic structure. As a general rule vaccines more than 3 months old should not be used. (4) When treating a case for a very long period the bacteriological diagnosis should be reconsidered in order to see if the flora has changed or become resistant to the action of vaccine administered. (5) Give the vaccine a thorough trial, specially in chronic cases. (6) Intercurrent illness, a long journey, a menstrual period, anticipation of a fatiguing or exciting time immediately after injection should lead to postponement of it. (7) Do not depend entirely on vaccine treatment but it should go hand in hand with other remedies recommended for any particular disease.

Dosage of autogenous and stock vaccines. For the amount and frequency of administration of a vaccine one should be guided by the clinical condition of the patient. There cannot be any fixed dosage in

the therapeutic use of a vaccine. The dose depends on the toxicity of the organism (of high toxicity 1 to 10 millions as initial dose, of low toxicity up to 100 millions), on the stage of the disease, whether acute, when very small doses are given, or subacute and chronic when large doses can be employed. The first dose is purely an experimental one and the subsequent doses must be controlled by the local, focal and general symptoms. The production of any marked reaction, either local or constitutional after any injection may be considered a contra-indication to any increase in dosage on the next occasion. A vaccine made with an organism of low toxicity may be increased by multiple progression whereas a vaccine made with organisms of high toxicity the increase should be by half arithmetic progression (e.g., 5-7½-10-15-20-30 millions). The time interval is another factor in the administration of vaccines. As a rule 2 to 5 days or 7 days interval between doses is given for chronic or subacute infections. But here again there is no hard and fast rule and one has always to be guided by the reaction of the patient. When stock vaccines are used the dose may be two or three times as large as those of autogenous vaccines and when used for prophylactic purposes they may be about five times the initial dose. It is convenient to prepare a vaccine of such a strength that the necessary first dose is contained in 0.1 c.cm.

Dosage, sex and age. Somewhat smaller doses should be used in females. In children under 6 years the adult dose should be divided by four, in children between 6 and 12 years it should be halved and from 12 to 16 years two-thirds of the adult dose should be given.

Prophylactic vaccines. Doses of most of the vaccines used for prophylaxis have been fixed more or less from previous experience. The least harmful and the smallest effective dose to protect a person from infection is administered.

General directions in the use of vaccines. Vaccines must be stored in a cool dark place. Vaccines should be well shaken before use and all aseptic precautions must be taken.

Administration. Vaccines may be injected intracutaneously, subcutaneously or in smaller doses intravenously.

The following vaccines are of proved value.

(A) *Prophylactic vaccines.* (1) *Cholera vaccine.* Dose—8,000 millions per c.cm. usually given in two doses of 0.5 c.cm. and 1 c.cm. at interval of a week. A single dose of 1 c.cm. may be used when necessary. (2) *Typhoid-paratyphoid (T. A. B.) vaccine.* Dose—Typhoid 1,000 millions, paratyphoid A. 750 millions, paratyphoid B. 750 millions in one c.cm. This vaccine is usually given in two doses of 0.5 c.cm. and 1 c.cm. at intervals of a week. A single dose of 1 c.cm. may be given when necessary. One dose of 1 c.cm. for re-inoculation. Sometimes Anti-T.A.B. and cholera vaccine are given together. (3) *Plague vaccine.* Three doses of 0.5 to 1 c.cm. at 8-day intervals. (4) *Anti-rabic vaccine.* Dealt with under the section on rabies. Only used for prophylaxis. (5) *Small-*

pox vaccine. Dealt with under the section of vaccination. Only used for prophylaxis. (See also page 778).

(B) *Vaccines used as therapeutic agents.* These may be either 'stock vaccines' or preferably prepared from the actual organism responsible for the disease and known as autogenous vaccines.

The following table is merely to be used as a guide to the initial doses of the vaccine for therapeutic use :—

Initial dose (millions)				Initial dose (millions)			
Bact. coli	20	N. pharyngis	20
C. diphtheriæ	10	Str. pneumoniae	10
Bact. Flexner	and	Flexner		Proteus group	20
group	20	Staphylococcus	50
N. gonorrhœa	25	Streptococcus	2
N. influenza	10				

Small-pox vaccination. The principle is to introduce *vaccinia virus* into the skin for inducing cow-pox and preventing small-pox. The material obtained from vesicles on a calf emulsified in glycerine or lanoline is used for the purpose. For detail see page 790.

VARICOSE VEINS. These are dilated, permanently lengthened and tortuous veins affecting mostly the superficial veins of the leg, spermatic veins and the hæmorrhoidal plexus in the rectum constituting piles.

The condition is due to some inherited weakness of the venous wall or irregularity in the arrangement of the valves or in cases of veins of the legs, some peculiarity in the lower fascial border of the saphenous opening. Besides these, other factors include persistent distension of a vein due to some pressure from above, such as, a pregnant or displaced uterus or a pelvic tumour; an abnormal communication between an artery and a vein may also result in a varicose condition of the latter. The tendency to varix increases with age and is favoured in old age on account of relaxation of the system resulting from sedentary habits.

TREATMENT. *Palliative treatment.* All sources of obstruction are to be removed. Massage is to be resorted to and the application of an elastic stocking or an India rubber bandage is useful in these cases. The bowels should be regulated and measures to promote general health should be adopted. Varicose ulcers and eczema are to be treated with soothing and drying ointments.

Injection treatment. The idea of injection treatment of varicose veins is to introduce some sclerosing solution of a drug to cause a chemical injury to the endothelium. It sets up a plastic thrombophlebitis without causing much pain to the patient whereby obliteration of the vein is also secured. The solution for injection should be cheap, easily dispensable, non-toxic, and should not produce any constitutional

disturbance. Further it should be sterile and antiseptic so that it does not produce any inflammatory changes at the site of injection. Prior to injection, the site is to be rendered surgically aseptic. The following solutions are used. (1) 30 per cent. lithium salicylate with 1 per cent. tutocaine (lithocaine). It is considered to be one of the best solutions and should always be freshly prepared before injection. The usual dose is 4 c.cm. The clot produced after injection is firm, hard and extensive with a minimum amount of local reaction. It produces local necrosis of subcutaneous tissues if the solution leaks outside and around the vein during the injection. (2) Quinine urethane solution contains quinine hydrochloride (B. P.) 60 gr., urethane 2 gr., and distilled water 30 c.cm. (Genevriev's solution). The dose varies from $\frac{1}{2}$ to 2 c.cm. Test for quinine idiosyncrasy should be made before the injection. The injection is painless and the sclerosis produced is extensive and permanent. A dose larger than 3 c.cm. should never be injected. The drawback of the injection is that untoward effects sometimes follow administration of quinine and an indolent ulcer may be produced if the solution leaks into the subcutaneous tissues. (3) Salt solution. The solution used consists of a 20 per cent. solution of sodium chloride to which 1 per cent. tutocaine has been added. This is suitable for small intradermal varicose veins only. Sometimes the solution is too strong for the veins, resulting in sloughing ulcers. (4) Sodium morrhuate. 5 to 10 per cent. solutions are used with the addition of 0.5 per cent. phenol as preservative. If 5 per cent. solution is used, $\frac{1}{2}$ to 1 c.cm. of it should be injected at different sites, three to four inches apart; the maximum dose should not exceed 5 c.cm. at one sitting. The tendency to production of an injection ulcer is less, but the end results are disappointing as they may show some degree of recanalization. (5) The 'twin injection' with quinine-urethane (2 c.cm.) and lithium salicylate 4 c.cm. injected from two separate syringes simultaneously at a distance of two to four inches in the same vein, are best practised on large tortuous veins. The results are satisfactory.

Contraindications to injection treatment are deep thrombosis of veins, phlebitis, pregnancy, advanced cardiac, pulmonary and renal disease, diabetes, marked cirrhosis of liver, generalised skin diseases. Complications of injection treatment are, injection ulcer, cellulitis, pulmonary embolism and infarction.

The results of excision of varicose veins have not been satisfactory in all cases. The scope of operation varies with the actual conditions present and the surgeon plans his operations on the merits of individual cases.

VERTIGO. The word vertigo means rotation and it is defined as a sensory disturbance with hallucinations of rotation, either of the patient (subjective vertigo), of his surroundings (objective vertigo) or both. Russell Brain holds that in vertigo the common factor in these hallucinations is the abnormal feeling of spatial disorientation,

no matter what plane they occur in and so he defines it as the sensation of a disordered orientation of the body in space. The nuclei and ganglia in the mid and hind brain are closely linked together and they all take part in the tone and position of the body, both static and kinetic. They are also in touch with the ear and eye and with the cornua of the spinal cord. The cerebellum and the nucleus of Deiters with their afferent vestibular influences are chiefly responsible for the symptom complex of vertigo. The cerebellum is essentially a co-ordinating centre for equilibration. Besides its afferent impressions from muscles and joints and the muscles of the head and eyes concerned in the maintenance of tone and balance of the body, the most important are those from the semicircular canals of the ear *via* the nucleus of Deiters. The semicircular canals form a sensitive register of stability and equilibrium. When stimulated, the labyrinths respond by external symptoms of vertigo, nystagmus and forced movements of the head and body.

ÆTIOLOGY AND CLINICAL TYPES: *Aural vertigo.* A systematic examination of the ear by the otologist is most essential. Wax in the external meatus, a blocked Eustachian tube, nasopharyngeal catarrh, middle ear disease, cholestromata, disease of the mastoid antrum, all should be borne in mind. A lack of patency of the Eustachian tubes with invagination of the tympana is a most potent cause of vertigo. Spasm of the tensor tympani or stapedius can also cause vertigo by disturbing the stapes. *Auditory vertigo* is not commonly produced by labyrinthine diseases but by other inflammatory causes and pressures from without or it may be entirely a reflex phenomenon. A patient with auditory vertigo experiences a sense of rotation either of himself or of his surroundings. As manifestations of cochlear disturbances, deafness and tinnitus might develop, nystagmus, forced movements, nausea and vomiting may also be seen. In Meniere's disease, the vertigo is severe and auditory in type. In the acutest form of the disease, the symptoms comprise giddiness, reeling, deafness, tinnitus, nausea, vomiting, cold clammy sweat, etc. Various causes have been brought forward to explain the syndrome but the ætiology is obscure. Meniere originally suggested that hæmorrhage into the labyrinth was responsible for the condition while others believe that this is due to a faulty water metabolism. The cerebral type of vertigo is less severe than the labyrinthine one. The common causes are cerebellar abscesses, tumours particularly in the posterior fossa, vascular cerebral lesions, etc. *Ocular vertigo* is due to a low degree of astigmatism, a strabismus of paralytic type and anomalies of muscle balance—heterophoria. A simple test of ocular vertigo is to ask the patient to open and close his eyes. If vertigo is present when the eyes are open, the vertigo is ocular and not aural. Cardio-vascular causes. Sudden cerebral hyperæmias or cerebral anæmia, organic heart disease with vasomotor failure, low blood pressure in convales-

cents, Stokes Adams' Syndrome and other arrhythmias are all predisposing factors of vertigo.

Miscellaneous causes. Vertigo is often complained of by neurasthenics and this is a common complaint of the female sex at the menopause. In disseminated sclerosis, a sensation of dizzy swaying is complained of. The vertigo which sometimes becomes severe and paroxysmal in nature is of pontine origin. Irritation due to intestinal parasites may be a reflex cause of vertigo. Of other reflex causes, diseases of the pelvic viscera in females deserve mention. The toxic causes responsible for the symptom are: intoxicants like tobacco and alcohol, drugs such as quinine, salicylates, the belladonna group and arsenic, bacterial toxins, syphilis, both the congenital and acquired types, herpes zoster of cranial origin. Mumps and influenza, as instances of acute toxic diseases, are known to cause severe vertigo. Epilepsy and migraine have also aura of vertigo. A small dose of quinine can differentiate an auditory vertigo from epileptic aura. It relieves the vertigo but not epilepsy. Finally, endocrine and vegetative disorders with unbalanced sympathetic and parasympathetic systems, should always be considered as potent causal factors of vertigo.

1. *Postural deviation.* The patient, with eyes closed and feet brought together, tends to fall towards the diseased side in irritative vestibular lesions. 2. *Kinetic deviation* (Barany's pointing test). The patient sits opposite to the physician and raises his arm, with the elbow straight, to touch the tip of the physician's finger with his own. He is then asked to repeat this with eyes closed. If the labyrinth on one side is paralysed, he tends to deviate or point past to the side of the lesion. 3. *Nystagmus.* Irritative labyrinthine lesions produce spontaneous vestibular nystagmus to the opposite side, that is, the eyes make a slow movement to the same side and a rapid twitch back to the opposite side. 4. *Rotation test.* The patient is seated in a chair which is very rapidly rotated for some time. The chair is then stopped and the patient looks in a direction opposite to that in which he has been rotated. Normally there is nystagmus in a direction opposite to that in which he has been rotated. 5. *Caloric test.* In this test, the tympanum should at first be inspected to see that it is not perforated and the external auditory meatus is free from wax and growths. The patient lies down and the external meatus is syringed with cold water (68°F). Cold air, blown through a coiled tube cooled by a spray of ethyl chloride, may also be used as a stimulus. Hot water (120°F.) is used when no response is obtained with cold stimulus. If the labyrinth is intact, the normal response to the stimulus is in form of a nystagmus away from the tested side. A hot stimulus generally results in nystagmus towards the tested side. If the nystagmus is not produced, there is a paralytic labyrinthine lesion.

TREATMENT. If the treatment is to be successful, a correct diagnosis of the underlying cause is most essential. The treatment of vertigo is therefore one of its primary cause. Luminal, in doses of $\frac{1}{2}$

to 1 gr. thrice daily, is of particular benefit in auditory peripheral vertigo. In severe cases, alcoholic injections have been tried. Marked success has sometimes been achieved by the section of the auditory nerve. In case of blockage of the Eustachian tubes, inflation by an Eustachian catheter should be resorted to. Tweedie reports encouraging results by using small doses of iodides (1 or 2 gr.) thrice daily when inflation or dilatation methods failed to cure or improve the condition. Very small doses of sulphate of quinine ($\frac{1}{4}$ gr. thrice daily) are very effective in diminishing the sensibility of the labyrinth. In cases of head injury resulting in concussion, a dose of 1/96 gr. of perchloride of mercury often relieves severe tinnitus and vertigo. Amyl nitrite gives relief in giddiness of arteriosclerosis. A salt-poor diet with restriction of fluid intake (40 oz. in 24 hours) and iodides should be the real sheet anchor in the disease. In neurotic cases, bromides such as bromide of sodium (20 gr. at night) afford prompt relief. The belladonna group of drugs is very helpful in sea-sickness. Chronic infections of the nasopharynx, tonsils, teeth, accessory air sinuses should be dealt with on usual lines. Various operations are performed to rectify disorders of the outer and middle ear. Pericarotid sympathectomy may be helpful in angiospasm. In intracranial diseases as increased tension due to growth, operation for decompression and other intracranial surgery may be resorted to. In the vertigo of acute toxic cases, relief may be obtained by ice cold water bottles applied over the occipital region.

VISCEROPTOSIS. Visceroptosis or Glenard's disease, denotes a syndrome characterised by an abnormal descent of the abdominal viscera with signs of irregular abdominal pains and dyspepsia. The descent of viscera is usually due to a fall in intra-abdominal pressure and is often associated with impaired tone of the abdominal and pelvic muscles. When the intra-abdominal pressure is abnormally low, the organs drop directly due to gravity and the degree of ptosis of different viscera depends upon their weight and also upon the length and elasticity of their peritoneal attachments which act as true ligaments for the support of the organs. A considerable amount of stretching and even damage is done to the abdominal and pelvic muscles during pregnancy and parturition in women and if sufficient rest is not enjoined, later on the tone of such muscles is permanently impaired. Weakness of abdominal muscles is also commonly seen in individuals who are not used to moderate amounts of exercise daily for the upkeep of health. In cases of malnutrition in conditions like rickets and prolonged pyrexia, degeneration and even atrophy of muscles have been marked.

* Sometimes the greater curvature of the stomach has been found after radiography to descend as low down as the true pelvis and the condition is then called *gastroptosis*. The condition has, however, been found to be congenital. Glenard has observed in *enteroptosis* kinks of

the intestine, especially at the flexures of the colon; pelvic cæcum and a low tranverse colon are often referred to as if they are invariably associated with constipation. In *hepatoptosis* the liver drops, rotates towards the right or sometimes falls forward so that its upper surface bulges in the epigastrium. In these cases the liver is not enlarged but is simply displaced. In case of a dropped spleen the organ can be shifted to its original position and such is also the case with the kidneys.

Various other causes have also been suggested for the displacement of abdominal viscera and the principal ones include a congenital mal-position, a pendulous abdomen with excess of intra-abdominal fat, and faulty postural habits. In all these cases the symptoms, if any, usually abate when the patient lies down and the organs resume their original positions.

The symptom is a vague pain experienced by the individual only when an erect position is assumed and is temporarily relieved when the lower part of the abdomen is compressed by some suitable means. Besides, signs of dyspepsia are often complained of by the sufferers. The symptoms are usually long-standing and ultimately the victims become neurasthenic.

TREATMENT. The condition in most cases can be prevented by suitable treatment. Prolonged rest combined with suitable diet and tonics go a long way to prevent the condition in parturient women. Constipation if any should always be corrected by proper purgatives. Graduated exercises should be taken by women to strengthen their abdominal and pelvic muscles, particularly after child birth. This helps to regain their normal postural tone and thus raise the intra-abdominal pressure. When the organs have dropped down low in the abdomen, some sort of support is required to hold them. A suitably fitted Curtis belt, serves the purpose well. Much comfort is then experienced by patients and most of the symptoms disappear. When the visceroptosis is due to weakness of the pelvic floor, exercise, local treatment by pessaries or even operation may be required to restore the tone of the muscles. In all these cases prolonged rest in bed constitutes the proper line of treatment. The normal routine should be gradually taken up by the patient only when symptoms subside. The diet should be of a mixed type including sufficient amount of proteins, fresh fruits, fats but not carbohydrate for symptoms of flatulent dyspepsia predominate in these cases. The meals should always be small but taken at frequent intervals so as to avoid over-loading of the stomach. The intake of fluids should be similarly restricted. Of the drugs, sedatives may be conveniently administered to neurasthenic subjects to calm their irritated nervous system and to promote sleep. If anæmia is present its treatment with iron, arsenic and other hæmatinic drugs help to restore the tone of the muscles and improve the general health of the patient. Massage,

both general and abdominal is highly beneficial in these cases. Electric treatment with sinusoidal current is helpful in restoring the tone of muscles. A change of climate is of immense value in improving the general condition of the neurasthenic subject. If medical treatment fails to relieve the patient surgical operations to restore the organs to their respective positions should be adopted as a last resort.

VITAMINS. See*page 176 and Appendix.

VOMITING AND NAUSEA. Vomiting or regurgitation of the stomach contents through the mouth is one of the emergencies sometimes required to be urgently attended to. The two symptoms of nausea and vomiting are common in many diseases where the latter is preceded by the former. Various causes may be grouped according to peripheral or central origin. Psychic impressions from unpleasant sights, odours or even thoughts, any profound emotion such as grief, anger or fear, count in a number of cases. Functional nervous disorders such as hysteria neurasthenia and psychasthenia are also held to be common factors in the causation of the symptom. Habit plays an important role in many cases. Diseases of the brain and its meninges, brain tumours, or cases of head injury are responsible in cases where it is of central origin. It also occurs in such diseases as dengue, malaria, cholera, scarlet fever, nephritis, migraine, and is a common symptom in sea-sickness, mountain-sickness and car-sickness. It is commonly met with in a variety of pathological processes in the abdomen such as appendicitis, intestinal obstruction, and diseases of the biliary apparatus and the urogenital organs. Irritation of the eyes, ears, nose, larynx, pharynx, oesophagus, stomach or the upper intestinal tract, is also a common aetiological factor. It is met with in pelvic diseases, disorders of menstruation and pregnancy in women. It is also seen after the toxic effects of anaesthesia, arsenic poisoning and uræmia. The prolonged intake of drugs such as digitalis, salicylates and morphine is also sometimes responsible for the condition. Vomiting in infancy is a common condition and the causes are middle ear disease, acute illness like pneumonia, cardiospasm, pyloric stenosis, over feeding, habit vomiting and worms. The actual act of vomiting is preceded by giddiness, salivation, rapid pulse and breathing.

TREATMENT. The treatment of all cases should aim at the investigation of the causal factors. Perfect mental and physical rest should be enjoined and the patient should be put to bed in a darkened room and excluded from noise, excitement, business cares and domestic worries. When sleep is induced nausea subsides in most cases. An ice bag to the head or sucking lumps of ice is often of distinct advantage. Many advocate the application of cold to the head and heat to the abdomen. Mustard poultices to the epigastrium have constituted a

favourite domestic remedy from time immemorial. During nausea there is usually more or less complete anorexia and as feeds by mouth are likely to aggravate the condition, parenteral routes are usually resorted to for the nourishment of the patient. The administration of saline and glucose combined with insulin is of particular benefit in these cases. A 5 per cent. glucose solution is an ideal feed during this time. Half to one fluid ounce of carbonated water or ginger ale every $\frac{1}{2}$ to 1 hour are useful drinks and are known to relieve the condition. As the condition improves a change of dietary may be instituted with the inclusion of strained soups, well cooked cereals and cereal broths or a suitable diet may be chosen according to the liking of the patient. In cases of protracted gastric vomiting washing out the stomach with $\frac{1}{2}$ per cent. sodium bicarbonate solution is sometimes very effective and this should always be tried when a toxin is suspected to be the cause of the condition. Tincture of iodine in 1 min. doses in a teaspoonful of water given every half an hour is sometimes useful. In cases of constipation and indigestion the bowels should be evacuated with suitable purgatives or preferably by an enema. The anti-emetic group of drugs include carminatives such as different forms of alcoholic beverages, spirit of peppermint and chloroform water, antacid, protectives including salts of bismuth and oxalate of cerium, sedatives, *e.g.*, bromides, chloral hydrate, morphine, barbiturates. The bromides are the best sedatives for all vomiting of central origin. They are said to depress the sensory centres and cut off the peripheral reflexes. Sodium bromide though containing a proportionately larger amount of bromine than the potassium salt is less active and is better tolerated by patients in heavy doses such as 15 to 20 gr. four times a day. Phenobarbital is extensively used for nausea, particularly in cases of pregnancy, in small doses about $\frac{1}{2}$ gr. three times a day. For local and peripheral action salts of bismuth, oxalate of cerium, cocaine and phenol are mostly used. The drugs are helpful in cases of irritation of the pharynx, oesophagus or stomach. Of the bismuth salts, bismuth subnitrate is usually given on an empty stomach in 30 gr. doses repeated every 2 hours till the condition improves. In nausea or vomiting of pregnancy, hysteria, epilepsy and migraine oxalate of cerium is used in doses of 3 gr. The local application of cocaine to the nasal mucous membrane has been recommended for the relief of nausea. The treatment of cardiospasm in infants consists in giving non-irritating diet and the occasional introduction of bougies through the cardiac-orifice. In pyloric stenosis daily gastric lavage is of benefit and surgical treatment affords a radical cure. Over feeding in children should never be encouraged and feeds should be served at regular interval.

WARTS (Verruca). The treatment of warts is very important as every practitioner is expected to deal with such cases in daily life. Warts may occur in every part of the body. The cause is obscure though it has been suggested that a filterable virus is responsible. These growths are

usually sharply demarcated from the surrounding skin. The chief symptom is pain on pressure. Warts should be distinguished from corns or callosities.

TREATMENT. Should aim at complete removal of the growth; if any portion is left, regrowth will occur. Drugs are of little value for the purpose. Caustics such as trichloracetic acid, nitric acid or pure carbolic acid have been used but are not suitable. Excision is likewise not desirable for uncontrollable bleeding may occur. The following are some of the agents that are commonly employed: (1) *Radium* application is the best method but it is not within the reach of every case. After such treatment, the wart becomes soft and uncerated and then separates leaving a cavity which requires filling with antiseptics for some time. (2) *X-rays*. A full pastille dose should be administered using a 1 mm. aluminium filter. The surrounding skin must be protected. Pain disappears always after treatment. (3) *Carbon dioxide snow*. Warts may be frozen with snow. The stick is held against the growth for $\frac{1}{2}$ to 2 minutes. Preceding such treatment the wart may be softened by prolonged hot fomentation or by the application of a 25 per cent. salicylic acid plaster about 24 hours before. If treatment is successful, the wart is found adherent to the blister formed by the snow. This should be cut away and the cavity is filled with bismuth subgallate powder or packed with cyanide gauze. (4) *Electrolysis*. It is difficult to ascertain the exact time of destruction of the growth with electrolysis and it is not recommended. (5) *Curettage*. A general anæsthetic, if warts be multiple, or a local anæsthetic like novocaine, may be used if a few only are present during curettage. All traces of warty materials should be scraped away with a sharp curette (Volkman's spoon). Bleeding is controlled with the galvano-cautery. The part is then painted with iodine and a dressing applied. If the patient complains of much pain, a 5 per cent. stovaine ointment may be applied. (6) *Vaccines* made from the emulsion of tissues may be tried along with local treatment. Intramuscular injections of bismuth salicylate (2 gr. in 1 c.cm. of sterile olive oil) have been favourably reported, only two doses are required.

WEIL'S DISEASE. It is a form of epidemic jaundice with fever, vomiting and hæmorrhage described by Weil in 1886. In 1915 the causal organism was isolated and is known as *Spirochæta ictero-hæmorrhagica*. The disease is probably of world-wide distribution but is most common and severe in Japan. It occurs widely among rats. The infection is believed to enter man by contamination of food and drink or probably by direct passage of the organism through the skin. Bites by infected rats may also convey the disease.

Diagnosis. (1) Presence of sudden fever, prostration, herpes and jaundice; about the third day hæmorrhages (epistaxis and mæna) often occur in severe cases. Rash on the body is very common. The

urine contains albumin and bile. (2) Blood, (a) *Leptospira* is present up to the fifth day, but is too scanty to be detected. (b) The blood count shows leucocytosis and secondary anæmia. (c) The platelet count is low. (3) Guinea-pig inoculation. Intraperitoneal injection of 3 to 5 c.cm. of the patient's blood produces jaundice, collapse and death of the animals in 24 hours after an incubation period of 6 to 13 days. (4) Urine is scanty and contains albumin, bile and blood, and *leptospira* are present after the tenth day. Guinea-pigs may be inoculated with the infectious urine.

TREATMENT. (1) Rest and fluid diet, general and symptomatic treatment. (2) The Serum of convalescent patients may be tried, dose 30 c.cm. daily. Serum of immunised horses has been used in Japan with success. (3) Urotropine given intravenously daily for 3 days in doses of 5 c.cm. of a 40 per cent. solution. (4) Intravenous injections of normal saline with 5 per cent. glucose are given in severe cases. Rectal saline may also be given. (5) Calcium is given for hæmorrhage.

Prophylaxis. Rat extermination, avoidance of infected soils, disinfection of hands, avoidance of public baths, etc.

WHOOPIING COUGH (Pertussis). It is an acute specific infectious malady characterized by catarrh of the respiratory tract, paroxysmal attacks of coughing followed by a long noisy inspiration (whoop) and signs of nervous disturbances. The disease is especially one of childhood, between the ages of 1 and 10 years. The period of incubation is from 3 to 14 days. According to Bordet and Gengou, the causal organism is a coccobacillus (*Hæmophilus pertussis*) which is present in the mucous membrane of the respiratory tract.

Diagnosis. (1) Clinically the onset is marked by a preliminary catarrh which lasts for 7 to 14 days. Towards the end of the period the cough assumes a paroxysmal character with occasional attacks of vomiting. Several paroxysms may occur in quick succession. Each paroxysm consists of a rapid succession of short coughs with open mouth and protruded tongue which are continued until the chest is emptied of air; relief is obtained by relaxation of the laryngeal spasm and the occurrence of the *whoop* (very diagnostic). As a result of coughing, large quantities of bloodstained stringy mucus are expectorated. (2) The presence of sublingual ulcers may be of assistance. (3) Leucocytosis is considerable in the early stage and the presence of lymphocytosis is of confirmatory evidence. (4) Bacteriological diagnosis by culturing the expectoration in Bordet-Gengou medium.

TREATMENT. (1) *Isolation* should be enforced, but free ventilation and fresh air are necessary. The diet should be light and when vomiting is present food should be given in small quantities at intervals. (2) *Drugs.* During the catarrhal stage a simple expectorant mixture is useful to control paroxysms. Belladonna in fairly large

doses (10 to 20 min. of the tincture) is the most effective drug; other sedative drugs are bromide, antipyrine, chloral hydrate. Benzyl benzoate has been recommended in doses of 5 to 40 min. of a 20 per cent. alcoholic solution 3 to 4 times a day; intramuscular injections of 1 to 2 c.cm. of ether are said to reduce the number of paroxysms, but the method is painful. (3) *Vaccines* prepared from Bordet-Gengou bacillus or associated with other organisms, have been used both as prophylactic and curative, but the effect is uncertain. (4) *Radiotherapy* is said to mitigate the severity of infection.

Prophylaxis. (1) The patient should be isolated for about 5 weeks from the commencement of the whoop provided the paroxysmal cough has ceased for a fortnight. (2) Disinfection of room and clothing. (3) Convalescent serum and vaccine may be used prophylactically.

YAWS (*Framboesia*). Yaws is a specific infective granuloma caused by a spirochæte, *Treponema pertenue*. It is not a venereal or congenital disease though the course resembles syphilis. The causal organisms *T. pertenue* gain access to the body through insect bites, cuts, abrasions, etc. Varieties of yaws are (1) Crab yaws: affects the sole of the foot. (2) Gangosa: granuloma ulcerating in the palate. (3) Goundou: a nodular swelling on the nose. (4) Juxta-articular nodules may form tumours near the knees or elbows.

Diagnosis. The primary lesion occurs extragenitally which is not always demonstrable. The secondary stage consists of development of papules which may coalesce into larger masses. Later the scales fall off, the characteristic raspberry-like granuloma forms, from which the name framboesia is derived. Yellowish fluid is exuded which dries, and forms a heaped-up yellow crust resembling syphilitic rupia. The spirochætes are generally found in abundance in the thickened epidermis. The Wassermann test is positive in practically all cases. It is distinguished from syphilis by the facts that the primary lesion is never venereal, the central nervous system is never attacked, the disease is not hereditary and it fails to yield to mercury treatment. *Laboratory diagnosis.* Clean serum that exudes after scraping the margin of the lesion with the blunt edge of a scalpel is examined for treponema either by dark ground illumination or made into a thin film and stained by Tribondeau's modification of Fontana's stain.

TREATMENT. For an adult 0.5 to 0.6 gm. of salvarsan intravenously or sulpharsenol intramuscularly. The lesions heal after 2 to 3 injections but it is advisable to give 6 injections at weekly intervals. Locally the sores should be dressed with mild antiseptics.

Prophylaxis. Isolate the patient and protect the open ulcers. (See page 655)

YELLOW FEVER. See page 990.

APPENDIX I

Appendix I contains upto date informations regarding certain subjects published since these sections were printed in the book. It is composed of abstracts from articles in journals and other works and should be read along with the subject matter dealt with on the pages indicated.

MALARIA

Atebrin in Labour Forces. The new synthetic drugs plasmoquine and atebrin have simplified the treatment and greatly reduced the relapse rate in malaria. Some of those who continue to use quinine admit that with atebrin there is a lower relapse rate, but they express their preference for moderate doses of quinine given for several periods of a few days each, their main object being not to cure the malarial infection at once, but to produce an increased resistance to the disease by allowing the sufferer to pass through a few mild attacks. Incidentally, this must produce a number of reservoirs for the spread of further malarial infection.

ROUTINE OF ATEBRIN TREATMENT (p. 605). The method followed in using atebrin is:—As soon as the patient enters hospital he is given a purgative—usually, for an adult, calomel 3 gr. followed by mist. alba, 2 or 3 oz. after a few hours. His blood is taken and the type of parasite determined. A dose of stock diaphoretic mixture three times a day until fever subsides helps to promote sweating and lessen distress. After the blood has been examined and a purgative and diaphoretic mixture given, the administration of atebrin is commenced. In proportion to age, children require bigger doses than adults. Each tablet of atebrin contains 0.1 gm. ($1\frac{1}{2}$ gr.); the dosage followed in ordinary cases is:—

Infants, up to $\frac{1}{2}$ a tablet daily.

Children of 1 to 3 years, from $\frac{1}{2}$ to 1 tablet daily.

Children of 3 to 5 years, up to $1\frac{1}{2}$ tablets daily.

Children of 6 to 10 years, $1\frac{1}{2}$ to $2\frac{1}{2}$ tablets daily.

Children of over 10 years, and adults, 3 tablets daily.

The temperature will usually fall to normal within 2 or 3 days.

If the temperature does not rise again above 99°F. after 48 hours, the atebrin treatment is continued for 5 days only. If the temperature stands above 99°F. at any time during the third or fourth day atebrin is continued for 6 or 7 days. Atebrin is not given for longer than 7 days in one course. When the malaria is subtertian in type a course of plasmoquine is administered after the atebrin treatment is completed:

plasmoquine has also been given in relapsing cases of benign tertian, but not in primary cases. The dosage of plasmoquine used for an average adult is 0.01 gm. tablet three times a day for 5 days—for a child of 10, half of a 0.01 gm. tablet three times a day for 5 days, and for a child of 6, one-third of a 0.01 gm. tablet three times a day for 5 days. Children under 6 years are not given plasmoquine without special orders. As regards atebirin for injection purposes, the earlier preparations were too insoluble. This difficulty has now been overcome by the production of a very soluble salt, known as atebirin musonate. It is a dimethanesulphonate of atebirin supplied as a yellow powder in sealed ampoules, containing 0.125 gm. each, corresponding to the single dose of 0.1 gm. of the atebirin bihydrochloride tablet for oral use. Each powder is dissolved in exactly 3 c.cm. of water before injection. The contents of one ampoule is the maximum single dose that should be given intravenously, but three times this amount, comprising one day's treatment, may be given intramuscularly at one time. The indications for the injection of atebirin musonate are the presence of high or persistent fever, severe vomiting, the advent of cerebral symptoms. In addition, it may be valuable for the rapid treatment of supervised cases in the course of a great epidemic. In Ceylon it has recently been tried in this way, 0.375 gm. (*i.e.*, the contents of three ampoules) being dissolved in 9 c.cm. of water and injected into the buttock daily in one dose on two successive days only. Blaze and Simeon claim that as a rule the fever and parasites disappear entirely after these two injections. The relapse rate, after such a short course, will probably be high. Atebrin is usually well tolerated by young and old, by infants, pregnant women, nursing mothers and persons in whom other diseases are complicated by malaria. Vomiting is rarer than with quinine; most patients prefer atebirin and many experience a sense of well-being and increased appetite during treatment.

Results. Under the treatment outlined the temperature is usually normal on the second or third day and seldom rises again above 99°F. In a proportion of cases the temperature is higher, and the parasites are more numerous on the second day than on the first day, owing to the provocative effect of atebirin on the parasites. All parasites usually disappear by the third day; and, except for crescents, none are found in any patient on discharge from hospital. As an exception, the temperature of one man with a subtertian infection remained above 99°F. for 216 hours though four injections of quinine bihydrochloride 10 gr., and four injections of atebirin 1½ gr. were given intramuscularly, and atebirin and quinine were used consecutively in treatment—each for 5 days. The average time spent in hospital when plasmoquine was not administered after atebirin was 7½ days; many patients were discharged in 5 days. When plasmoquine was given separately after atebirin the patient was sometimes in hospital for 10

or 11 days, though part of this after-treatment was occasionally given in the lines.

PLASMOQUINE AS AN ADJUNCT TO ATEBRIN TREATMENT. Atebrin treatment by the eradication of schizonts prevents the formation of later generations of gametocytes. The earlier broods of gametocytes will die out in a few weeks. Whether plasmoquine should be given to kill the latter, depends therefore on the risk of infection being conveyed to others in any particular estate. In this several factors are involved; the number of persons with gametocytes in their blood; the number of malaria-carrying anophelines present (most important), the number of bites received from infected mosquitoes; the intensity of the infection conveyed; the effectiveness of the antimalarial work. A change in the level of the surface water, an influx of unhealthy new labourers or the clearing of new area may necessitate the adoption of measures not previously needed. The League of Nations Malaria Commission's Report (pp. 236-237) suggests that the percentage of malarial cases containing gametocytes in their blood may at times be as low as 1 per cent. though in children it may be 17 per cent. or more. But Green, in a series of 1,000 sub-tertian cases found that over half carried crescents in the proportion of 1 or more per 200 leucocytes and were therefore potentially infective to *Anopheles maculatus*. If these high rates are common the argument for giving plasmoquine is strengthened. Green found also that gametocytes seldom appeared before the 6th day in new infections and took on an average nearly 8 days to disappear under treatment with plasmoquine compound—the limits being 4 to 13 days. It may be assumed therefore that the treatment with plasmoquine simplex should not be started before the 6th day in primary attacks, and that with an adult a dosage of from 0.02 gm. to 0.03 gm. daily should be continued for from 5 to 7 days.

USE OF ATEBRIN FOR PROPHYLAXIS (page 607). The recent Report of the League of Nations Malaria Commission stresses the fact that quinine, even when given in the fever-free and parasite-free period just before a relapse, exhibits a lack of therapeutic action. Also, a considerable proportion of persons with enlarged spleens, chiefly of the fibrotic type, harbour no parasites at all, and some of them have acquired an immunity. The routine use of quinine for enlarged spleens has now been abandoned: atebrin treatment has been substituted for selected cases only—especially for new locally-engaged labourers who have either a recent history of malaria, parasites in their blood, or a temperature. No treatment is given to those with fibrotic spleens nor to any who have already received a course of atebrin for malaria, and who show no relapse, symptoms on examination. Acting on these lines a prophylactic course of atebrin was given, to about half of 962 persons found with enlarged spleens at special examinations in 1933, and to a similar proportion in 1934. Those who appeared ill were put in hospital, but the majority remained at work and received a 5 day's course of three tablets

daily given in one dose after they had come in from the field; no ill effect were observed. Wallace, working in Kedah, finds atebirin is the most effective drug for mass treatment at the beginning of the malarious season. In 1933, on one of his estates where malaria was seriously affecting the labour, no cases occurred within a month after a 5 days' mass course of atebirin and the malaria rate remained low for the two succeeding months. On another malarious division where the parasite rate was 18 per cent. amongst adults and 23 per cent. amongst children, a 5 days' course of atebirin and plasmoquine reduced the parasite rate to nil. After this 0.02 gm. plasmoquine was given three times weekly for 3 months, at the end of which the parasite rate was: adults 3.5 per cent., children 5 per cent. These doses of plasmoquine will inhibit the sexual forms and thus prevent infection of others.

COST OF ATEBRIN TREATMENT. Green states that atebirin is the cheapest drug for treating malaria if labourers are not subject to frequent reinfection, because it is superior to quinine both for destroying benign tertian and quartan gametocytes and for preventing relapses. It has no effect on sub-tertian gametocytes, for the destruction of which plasmoquine must be given. In two large comparative series of cases from the same estate, Green found that the percentage of days spent under treatment per unit of population, including a preliminary mass treatment, was atebirin 7 per cent., quinine 27 per cent. With atebirin the relapse rate was much lower, the working efficiency was maintained at a high level, and far fewer working days were lost. During the past 3 years in Malacca, the cost of a 5 days' course (15 tablets) has varied between 72 and 89 Straits cents (1s. 8d. to 2s. 1d.). Allowing a 15 per cent. relapse rate for which 12 cents may be added, the maximum cost per head is just over \$ 1 Straits (2s. 4d.). During the same period the price of quinine sulphate has varied from \$ 14.50 to \$ 17 Straits, and of quinine bihydrochloride from \$ 19 to \$ 24 Straits per pound. Taking into account the much higher relapse rates with quinine, not less than 1 oz. is needed for an average complete treatment on estates. The additional cost of 0.15 gm. of plasmoquine given in a 5 days' course is 43 Straits cents (1s.); which course is advisable, at any rate in subtertian infections whether atebirin or quinine has been used. While the total drug treatment with atebirin actually costs less than with quinine in properly supervised cases, there is a still greater saving effected by the low relapse rate lessened absence from work, and the greater efficiency following atebirin; the shortness and simplicity of administration is a further point in its favour. Atebrin is the best drug available for the controlled treatment of all types of malaria in Malaya, where effective oral administration is preferable to injection. (*Trans. Roy. Soc. Trop. Med. & Hyg.* 1935, Vol. 29, No. 3).

Toxicity of Atebrin (see page 608). Owing to the very slow excretion or destruction of atebirin in the body it seems unnecessary

to exceed the dose of 0.1 gm. for an adult for intravenous injection. The margin of safety is probably not great, and intravenous injection should be resorted to only in emergency. The injections should be made very slowly and timed to take several minutes for completion. The total injected over a period of twenty-four hours should not exceed 0.3 gm.

Untoward effects of atebtrin appear to include: gasping or accelerated respiration, circulatory failure, collapse, vomiting, possibly rise of temperature, psychoses, loss of appetite and of weight, abdominal pain, headache, diarrhoea, yellowed sclera, rather persistent yellowing of the skin. Recently various writers have drawn attention to symptoms varying from mental excitability and psychoses up to temporary insanity, after the use of the drug. Disordered mental conditions are well-recognised sequelæ of the treatment of malaria with atebtrin and numerous such cases have been seen during the recent epidemic of malaria in Ceylon. The onset of symptoms generally occurs towards the end of, or immediately after the usual course of 15 atebtrin tablets. Kingsbury (1934) published a record of seven cases of psychical neurosis in malarial patients treated with atebtrin in the Malay States. In the majority of cases the mental disturbance appeared after the usual dosage of atebtrin 0.1 gm. thrice daily for 5 to 7 days, but was generally of short duration. In a more recent publication Udalagama (1935) reports another series of seven cases of mental disturbance in a total of 644 cases after treatment with the standard course of atebtrin (two intramuscular injection of atebtrin musonate, each equal to 0.3 gm. of atebtrin). In five cases mental symptoms developed after the maximum therapeutic dosage in a child aged 8, it followed after two doses of 0.16 gm., and in the other after a single dose of 0.2 gm. Hay and others (1935) used the drug both parenterally and by the oral route in smaller doses and found that mental excitability after atebtrin is rare and when it occurs is easily controlled by sedatives.

The mode in which cerebral symptoms are brought about by atebtrin is not yet understood. It should be remembered that cerebral excitation and more serious forms of psychosis may arise as complications of severe malarial infection itself or they may be due to the action of atebtrin on the central nervous system. There seems, however, to exist some ætiological connection between the mental disturbances and the administration of atebtrin in malarial patients. It is quite possible that following the administration of large effective dose of atebtrin, a sudden liberation of toxins may occur in the tissues as a result of direct lethal action of the drug on the parasites, with consequent production of cerebral symptoms. In addition, a non-toxic dose may sometimes produce toxic affects in certain individuals whose tissues have been damaged by a malarial infection. Whatever may be the exact way in which this is brought about there are certain factors such as age, sex, race, individual resistance, which play a great part in the causation of

symptoms. It has been observed that with oral administration these symptoms are rare; with a moderate parenteral dose (0.15 gm.) they are still comparatively rare and are easily controlled with sedatives, but with larger doses (0.3 gm.) they more frequently occur and tend to be more serious and prolonged. Experience has shown that if the dosage of atebirin is increased above the optimum, the chances of untoward symptoms occurring are increased. A five-day course of atebirin with 0.3 gm. of the drug in divided doses daily as is now used, seems to be a dosage with a considerable margin of safety.

In view of the very slow excretion or destruction of the drug in the body, it has been suggested that a course of treatment with it should not be repeated within a period of, say, eight weeks, and that the drug should be taken only under supervision of a physician.

Totaquina (p. 549). Totaquina is a mixture of cinchona alkaloids prepared according to the formula of the Malaria Commission of the League of Nations. There are two types—Type I and Type II. The report of the Health Committee of the League of Nations (1934) deals with the results of trials with these two varieties on the lines suggested by the sub-committee and with supplies of totaquina provided by them, in a number of malarious countries. Totaquina is not intended to replace quinine, but it is hoped that the use of mixtures of the alkaloids will enable the treatment to be extended among the masses, as these mixtures are likely to be less expensive than pure quinine.

The results of the trials in the different countries have been analysed critically by Fletcher at Kuala Lumpur. Parasite-counting methods were employed in evaluating the treatment with totaquina and at the same time a control series of patients was treated with quinine. The records of the cases analysed, clearly show that totaquina acts like quinine as a potent remedy in all forms of malaria. But the opinion expressed is that a field trial of this kind is not a carefully controlled experiment and when it comes to deciding whether totaquina is a little better than quinine or not quite so good, one is on less sure ground in the absence of adequate controls treated with quinine. The observations made at the different centres were not sufficiently precise and unanimous to warrant a final decision on the relative merits of the different samples of totaquina. As regards toxicity, sufficient evidence was not forthcoming to show that totaquina is more toxic than quinine in the doses given. The findings of the Health Committee after examining this report is that totaquina seems able to fulfil the purpose for which it was intended since its efficacy is equal to or only slightly less than that of quinine.

Hicks and Diwan Chand (1935) performed experiments in India with two types of totaquina. The trial was carried out on the lines suggested by the Health Committee. More than 250 patients were treated and if the untreated control group is excluded, there was an

average of 40 patients in each group and no group contained less than 31, so that in point of numbers it may be considered an important series. The quinine and both types of totaquina for these experiments were supplied by the Madras Government Cinchona Department. The composition of the two types are given below :—

		Type I per cent.	Type II per cent
Quinine	...	32	19
Quinidine	.	1	4
Cinchonine	..	11	20
Cinchonidine	.	30	26
Amorphous alkaloid	...	15	19

The tablets of totaquina each contained 0.25 gm. of the alkaloids. A dose consisted of one or more whole tablets together with one tablet cut down to a size estimated to complete the correct total dose. The conclusions of these workers are that under experimental conditions there was no distinct difference in efficacy between quinine and the two types of totaquina in clearing the blood of parasites either in benign or malignant tertian malaria.

Russell and his co-workers, have on a small scale, carried out an examination of the problem of the treatment of malaria in the Philippines, from the economic, the botanical, the chemical and the medical points of view. From clinical trials reported in this paper the conclusion that can be drawn is that given in the doses in which quinine is usually employed, totaquina is an efficient anti-malarial drug. The final conclusions at which these writers arrive are given in detail because it is thought the problem of treatment of malaria in India is very similar :

"It is not improbable that if every case of malaria occurring in one year in the Philippines could be given a 250 gr. treatment there would be needed at least 30,000 kilo. more specific febrifuge than is now imported.

A 250 gr. treatment with quinine sulphate in the provinces costs from 2.50 to 5 pesos (1.25 to 2.50 dollars United States currency). The greater the need, the higher the price. Quinine dihydrochloride retails for from two to four times as much as the sulphate. These retail prices are far more than the average farmer in the provinces can pay. Quinine and the synthetic drugs, plasmochin and atabrin, may therefore be called a rich man's remedies. There is no probability that much more quinine can be paid for than is now imported.

The Bureau of Forestry has demonstrated that cinchona will grow in the Philippines and will give as good a yield of alkaloids as that

grown elsewhere. From our studies we conclude that the standardised total alkaloid extract of cinchona, recommended by the Health Organization of the League of Nations and called 'totaquina' can be prepared locally from Philippine cinchona easily and inexpensively.

We conclude from some clinical tests that this Philippine totaquina is probably about equal to quinine sulphate in its therapeutic value against malaria.

We conclude that, allowing a fair profit to the grower of cinchona, the manufacturer of totaquina and to the retailer, this Philippine totaquina could be sold to the people at not more than 35 centavos (0.175 dollar) per 250 gr. treatment.

Contrasting 35 centavos with the present retail price of from 2.50 to 5 pesos for a 250 gr. treatment with quinine sulphate or atabrin, we conclude that the local production of totaquina would materially aid in combating malaria in the Philippines.

We also conclude that the growing of cinchona and the manufacture of totaquina might have considerable economic importance to the Islands, being capable of becoming sizeable new industries."

The foremost consideration is now to inaugurate a policy of cinchona cultivation that will eventually place a cheap and at the same time efficient mixture of alkaloids in the hands of malaria-stricken masses of India. (*Ind. Med. Gaz.*, 1935, Vol. 70, p. 567. *Record of the Malaria Survey of India*, March, 1935).

Review of Report of the Malaria Committee of the League of Nations.

TREATMENT OF PRIMARY ATTACKS (p. 617). In selecting the best treatment for an attack of malaria the Commission say that "Quinine has no appreciable effect when given during the incubation period, and it has little effect when given on the first or even the second day of the 'initial fever'. It is much more effective after the patient has had several paroxysms of fever than at an earlier stage, and its effect is greatest when fever and parasites are beginning to decline as a result of the natural defensive mechanism which normal human beings possess" (p. 209). This and other statements found in the report lead one to believe that the Commission advocates that the patient should be left untreated for some days during the primary attack. Such a procedure may be all right under experimental conditions found in mental hospitals but would not be possible under ordinary hospital conditions in malarious countries. Even in induced malarial practices in hospitals where there is insufficient attention to the blood condition, the fatalities due to this strain of benign tertian malaria are not less than 10 to 14 per cent. (p. 217). Such a procedure therefore is likely to be very dangerous in general practice where there is no indication of the virulence of the infecting strain, nor can it be determined with certainty that a mixed infection is present or not.

Sinton and Mulligan (1933) have fully gone into this question and state: "James (1931) reports that the therapeutic action of quinine in benign tertian malaria is considerably enhanced, if the patient be allowed to develop a certain degree of tolerance to the infection before treatment is commenced. He, however, remarks that "it would be unjustifiable at present to withhold quinine from a case of malignant tertian malaria later than the first discovery of parasites in the blood. It appears to us that, in view of the not uncommon occurrence of unsuspected mixed infections in malarial patients in the tropics, one is seldom or never justified in allowing any malarial infection to remain untreated in the hope of obtaining this degree of acquired immunity. It was found by Antic (1925) that in experimental mixed infections with *P. vivax* and *P. falciparum*, the former parasite could be detected at a very early stage of the infection, but that the latter quickly predominated. The more conspicuous morphology of *P. vivax*, and its presence in the peripheral blood during the whole of its schizogony cycle, make it much more easily detectable than the small rings of *P. falciparum* which are usually present in the circulating blood for a much shorter period of each cycle. The latter parasite might, therefore, be overlooked during the first few paroxysms of an acute attack. The difficulty which is sometimes experienced in detecting *P. falciparum* in some early acute cases, has been noted by many workers, even when there has been no mixed infection to obscure the issue. If the patient remains untreated, in the hope that the more benign parasite may produce some tolerance to aid the effect of treatment, the unsuspected infection with *P. falciparum* may quickly predominate. Daily blood examinations are usually impossible under the conditions of general practice in the tropics. If treatment be withheld on the assumption that the primary diagnosis of *P. vivax* is correct, the rapid development of *P. falciparum* may remain undetected until therapeutic measures are too late to save the life of the patient, or at least to avert a pernicious attack."

"While believing that some degree of acquired tolerance probably augments the action of quinine, we do not think that patients can be left, as a routine measure, untreated so that such tolerance will develop. At least it does not seem a wise procedure in areas where *P. falciparum* is common. The shortage of hospital accommodation and expert medical supervision in many tropical areas also precludes this method as a routine step, however desirable it may be under the more carefully controlled conditions of therapeutic malaria."

"The work summarised by Mulligan and Sinton (1933) also suggests very strongly that any immunity, thus acquired, may only be effective against the same strain of parasite, and will have no very marked effect if the patient be reinfected with another strain. Now that several of the new synthetic drugs have been found to have a marked curative

action in chronic infections with *P. vivax*, the necessity for leaving malarial patients untreated in his fever seems to have disappeared to a very large extent."

It will thus be seen that delaying the treatment is not a measure which can be justifiably recommended for use in the majority of hospitals in the tropics nor for practising physicians of any country.

TREATMENT TO PREVENT RELAPSES. The Commission have endeavoured to indicate the principles by which the physician should be guided in selecting a system for preventing relapses (p. 233). It says:—"The frequency and severity of relapses are dependent chiefly on the amount of defensive power which the infected person possesses naturally or acquires as a result of previous attacks. A scientific method of preventing relapses should be based on this knowledge or should take this knowledge into account by allowing an infected person to acquire as much defensive power as possible. Persons who are treated with large doses of quinine or other specific drug at the first onset of fever in their primary attack and in each relapse get no opportunity of acquiring defensive power to prevent relapses. Persons who are so treated usually relapse every month for a very long period. During the primary attack, it may not be safe to abstain for a day or two from giving a specific drug, but it is quite safe to do so in the first and any subsequent relapse."

"In a scientific system for the prevention of relapses, no attempt is made to give 'treatment for the prevention of relapses' during the primary attack. One waits until the first recrudescence and then uses the specific remedies in such a way that they will assist, rather than hinder the development of the patient's natural defensive forces. By repeating this plan with the same watchfulness during the second recrudescence (using the specific drug at a later period and more sparingly than in the first recrudescence) and again, if necessary, during the third recrudescence, it happens, in most cases, that the patient becomes fortified or premunised against the disease to the extent that he not only ceases to suffer from relapses but fails to have an attack when he is 'reinfected'. In the Commission's view, an endeavour to follow that plan should be made for the prevention of relapses of benign tertian and quartan fever. But they consider that, for preventing relapses of malignant tertian fever, it is justifiable to endeavour to sterilise all the parasites by specific drug therapy during the first recrudescence" . . . "The Commission believes that, when it is not justifiable or practicable to prescribe a system for the prevention of relapses, which is based on the above principles, the best practice is to adopt a system of 'clinical prophylaxis' consisting of the administration of a small dose of quinine (0.4 gm.) daily throughout the period of residence in the malarious country and for several months after leaving" (p. 233).

That some degree of acquired immunity is of importance in controlling the clinical manifestations of a malarial attack is probably correct. This acquired immunity probably also assists in the radical cure of the disease specially when helped by the effects of appropriate specific therapy. In certain infections, however, in spite of opportunity for developing high degree of tolerance and specific therapy of a certain nature relapses may continue to occur for long periods. The failure in producing a radical cure is not due so much to a low degree of immunity as to a special resistance of the parasite to the destructive action of the specific drug used. In such cases the obvious thing should be to change the specific drug rather than allow the patient to continue relapsing for months in the hope of obtaining a higher degree of resistance, and so a tolerance which may be broken down at any time by adverse conditions.

It is stated that "the patient becomes fortified or premunised against the disease to the extent that he not only ceases to suffer from relapses but fails to have an attack when he is reinfected." In this connection the work of Sinton and others has shown that in human simian and avian malaria, an immunity such as has been ascribed to one strain of a species of plasmodium, may have little or no effect in preventing acute attacks when the host is reinfected by either heterologous strains or species of parasite. A patient would therefore have the acquired immunity to all the local strains of the parasites, a process which probably takes some years during which he would be in a continuous state of ill-health. It would appear, therefore, that an attempt to develop the premunition is not advisable for patients whose period of residence in a malarious country is short, or who are living under conditions in which the chances of reinfection can be avoided.

DELAYED TREATMENT DURING RECRUDESCENCE OF RELAPSES. The Commission considered that there is little danger to the patient's life on the occurrence of a recrudescence or a relapse of a primary infection. It is suggested that the patient should be allowed to have several febrile paroxysms, and that the amount and duration of specific treatment should be small so that the natural process of premunition may not be interfered with. It is well known that a considerable percentage of malarial infections are radically cured by the treatment given in the primary attack. In induced malaria the reappearance of fever and parasites is undoubtedly a recrudescence or relapse but this is not so under natural conditions in malarious places. In very malarious localities a patient who gets a malarial attack sometimes after the termination of treatment for the primary attack may be a fresh infection with a heterologous strain or species of parasite and not necessarily a relapse. Such an infection may give severe clinical manifestations. If such a case be treated by the method suggested by the Commission, for a recrudescence or relapse or a primary infection, the small dosage

and the delayed administration of the specific drug may allow such serious developments in the infection that it may be too late to save the patient's life, when proper treatment is instituted.

SEPARATE TREATMENT FOR ACUTE ATTACKS AND FOR RELAPSES. The Commission considers that "It is seldom or never in the best interests of patients to endeavour to combine a plan of treatment designed for the prevention of relapses with a plan having for its object the rapid clinical cure of an acute attack (p. 214). The two problems (cure of primary attack and prevention of relapses) are so entirely different that, in the opinion of the Commission, it is incorrect to endeavour to accomplish them both at the same time" (p. 215). Such a dissociation of the two treatments may be possible and advisable under conditions of therapeutic malaria, but in the tropics and in most malarious countries this would not be possible. The clinical effects of atebirin and quinine are apparently very similar, and there would not seem to be much advantage in administering them at the same time, to produce greater effect in the production of a radical cure. Some authorities consider plasmochin to be of very great importance in preventing relapses of benign tertian malaria when combined with quinine, so that they could be combined in the treatment for a radical cure of this infection.

CLINICAL PROPHYLAXIS. "Clinical prophylaxis is correctly defined as being a procedure for curing slight clinical attacks of malarial fevers—it is a curative, not a prophylactic measure" (p. 204). "The Commission is of opinion that quinine is effective for this purpose and that it is the best drug to use. The correct plan is to take a daily dose of 0.4 gm. (6 gr.)." Although it is quite likely that beneficial results with regard to morbidity and mortality may be obtained in malarious areas by this plan, such a plan cannot be put into practice among the undisciplined and uncontrolled population. Even if it was, the expense of the drug and the cost of distribution would make it prohibitive. Sinton obtained good results in lowering malarial morbidity and inefficiency among troops in India by this measure but the plan is wasteful and expensive.

One of the reasons given by the Commission for its advocacy of this method of clinical prophylaxis is that "it does not entirely eradicate the infection, the defensive mechanism of the body is continuously at work and becomes increasingly powerful as time goes on ('acclimatisation without risk')" (p. 235). If the defensive mechanism of the body is stimulated by the parasites, it may be argued that a much more powerful stimulus would be given if they were destroyed only when they were sufficiently numerous to produce fever (*i.e.*, when fever is imminent) rather than being continually kept at a very low level. If the benefits of clinical prophylaxis after a single infection are thought to depend mainly upon an increased defensive action of the

body, its benefits would, theoretically only be applicable to one strain of one species of parasite only, for the defensive action against a single strain should have little or no effect upon superinfection with a heterologous strain of plasmodium. According to the Commission, clinical prophylaxis should have no action in the prevention of superinfections, because it says that "quinine, even in curative doses, has no true causal prophylactic action."

Clinical prophylaxis may however be of greatest practical value under those conditions where it can be properly carried out. Such a system of treatment may be recommended when large bodies of people are sent into areas in which they have little or no immunity against the local strains of parasites, and it is desired that as few persons as possible must develop clinical manifestations of malaria during their stay in the area. The good effects of this method appear to depend on the fact that the number of parasites in the patient's body, as the result of infection and reinfection are kept below the limit of producing paroxysms. It is really an early clinical curative treatment. This method may help the individual to develop a considerable degree of immunity to reinfection or superinfection with local strains or species of malaria. The cost of such a daily dosage with the specific drug would be prohibitive.

General Principles of the Therapeutics of Malaria, with Special Reference to the Masses in India. The Commission in their report have dealt with modern therapeutics of malaria from "the point of view of persons who are in a position to obtain medical advice and efficient care rather than from that of the mass of the population of malarious countries" (p. 277). The vast majority of the millions of malarious sick in India however, are not in a position to obtain such advice and care, and it is probable that the same holds good for many other malarious countries. For the application of such therapy, infected populations may be divided into two main groups, in which, as judged in the light of our present knowledge, the object of treatment is distinctly different. These groups are—(a) those individuals in whom the risk of reinfection is relatively slight or absent, because of environmental factors, or of antimalarial measures of various kinds. In individuals situated under these conditions, one should aim at the production of a radical cure of the infection at the earliest opportunity, and by such methods as have been discussed above, or by such new methods as may be considered suitable.

If such persons are not liable to reinfection at frequent intervals, there appears to be no object in allowing them to acquire, by prolonged latent infection, an immunity which would be of value only against the infecting strain. The chances are that they may be infected on the next occasion by a heterologous strain or species, against the clinical effects of which their hard-won immunity may have little protective power. Under such conditions the patient will have suffered,

to little advantage, the long series of relapses and recrudescences advocated by the Commission.

In the production of radical cures in such individuals, wherever possible the treatment for clinical cure and that for radical cure should be combined. In this way the period of morbidity and inefficiency would be cut down to the minimum.

Sinton considers that both from the point of view of economy and because of their marked action on malarial infections, quinine or some of the other cinchona alkaloids should form the basis of all such "standard treatment." The newer drugs have in some cases advantages which the cinchona alkaloids do not possess, but they have also disadvantages not shared by those alkaloids. Such new drugs can only be considered as adjuvants to the action of the cinchona alkaloids, more especially because of their relatively high cost, which places them beyond the reach of the majority of patients. Therefore where possible, the adjuvant action of these and other drugs should be taken advantage of, in treatments which aim at a rapid clinical cure. Certain drugs can with advantage be used in combination with the cinchona alkaloids, while others may be substituted for them in those infections which for any reason have proved refractory to the radically curative effects of quinine, alone, or in combination with certain adjuvants.

Individuals who are liable to reinfection or super-infections within a very short time after the termination of treatment. There is much evidence to support the view that when, by natural or therapeutic means, an individual is radically cured of an infection with one strain of parasite, irrespective of its species, he rapidly loses most of any acquired immunity or premunition which he has developed to this strain as the result of his infection. The evidence available suggests very strongly that to maintain any high degree of such tolerance to the clinical effects of infection, it is necessary that the individual should continue to harbour the parasites of this strain, *i.e.*, that his defensive mechanism should be continually stimulated either by the parasites of a latent infection of the strain, or by continued re-inoculation with the same strain.

In view of these facts it would seem that the production of a radical cure under conditions where reinfections are frequent, is contra-indicated. Such cures of the infection would, theoretically at least, leave the patient more liable to severe clinical attacks, if the intervals between the reinfections with the same strain of parasite were greater than the duration of his immunity after radical cure.

In so far as Indian conditions are concerned, Sinton (1935) says:—
 "Most of the uncontrolled rural population of India have (a) no wish

to continue treatment after the fever and clinical manifestations of malaria have disappeared and (b) have not the financial means to pay for the cost of a treatment which might produce a permanent cure of the infection that is troubling them at the time. Even if they could be cured, the chances of reinfection at a comparatively early date are great in many places. Under such conditions of liability to reinfection, the attempt to produce a permanent cure seems futile and indeed may have unfortunate effects. As pointed out in our monkey experiments and as noted in malarial investigations in Europe, the patient who survives an attack may develop an immunity to the strain of parasite which infects him, and this immunity may act as a considerable protection against another infection with the same strain. Such latent infections under ordinary conditions do not produce very severe clinical effects, and such as are produced are usually easily controlled by a little treatment. As we have not solved the problem of the prevention of reinfection among the rural population, *i.e.*, the destruction of the infected insect host, or means for preventing the transmission of the disease by it, attempts to produce a permanent cure of the infection appears to be a waste of money in most cases."

"Under these conditions, in my opinion and in our present state of knowledge, the objects to be aimed at are (a) to make available suitable treatment which every sufferer can obtain, either free or within his financial means and (b) to ensure that such treatment can be obtained by the patient with ease in whatever place he may be. The result of such provision would be that a sufferer from a malarial attack would have treatment available, and thus (i) diminish the risk of a fatal result, (ii) diminish the intensity and duration of the attack, and (iii) curtail the period of physical disability."

Such a system of clinical cure among populations liable to reinfection, should not interfere radically with the development of their "tolerance" to the clinical manifestations with infections of the local strains, nor in the presence of continual reinfection should it interfere seriously with any immunity already acquired.

This power of developing tolerance appears to be present to a different degree in different races. As has been proved by experiments with induced malaria, the degree of individual susceptibility to the clinical effects of malarial infection in previously uninfected persons, may vary very considerably. It would also appear from field observations, in various parts of the world that certain races may possess a considerable degree of so-called "natural immunity" to malarial disease, as compared with other races. It is possible that through very many centuries of exposure to intensive, untreated malaria, persons with a greater susceptibility to the disease would be more liable to death in childhood, and would be weeded out. So the race would be continued by survivors (the adults) having a more marked degree of tolerance

or power to develop such tolerance rapidly. (*From Col. Stinton's writings*).

NON-SPECIFIC COLITIS

Non-specific colitis usually refers to the condition which is characterised by diarrhoea with blood and mucus in the stools, but is unassociated with dysenteric or other recognised infections. No specific cause has yet been found. It is probable that a variety of causes may be responsible for this condition.

The outstanding change in the bowel is an inflammation of the mucous and submucous coats, strictly limited to the large intestine, especially the descending colon. The changes in the mucosa follow the usual sequence of acute inflammation, ulceration, fibrosis, and local proliferation leading to polyposis. The normal function of fluid absorption by the colon is interfered with, which in later stages may give rise to incurable diarrhoea. The clinical course of the disease is very variable and is characterised by periods of remission.

TREATMENT. Various therapeutic trials have been made in the past and the observations on their results are noted below.

1. *Treatment by irrigation of the colon.* It is based on the view that the condition is caused by an infection which lies in the mucous surface within reach of the irrigating solution. It is a common practice to order lavage with disinfectant solutions. Sometimes appendicostomy or caecostomy is carried out to facilitate a thorough washing out. These irrigation methods have often proved unsuccessful and in certain cases have aggravated the condition. The tissues of the colon are highly sensitive to trauma in colitis, treatment by colon lavage therefore often does harm and surgical procedures are contra-indicated in acute colitis.

2. *Treatment with sera and vaccines.* The use of anti-dysenteric serum and of Bergen's specific streptococcus serum and vaccine have been much employed. Hern (1931) found that about 50 per cent. of the cases appeared to benefit by the treatment. The results are probably due to a non-specific protein reaction. Bergen's streptococcal serum and vaccine do not produce a specific curative reaction and the effect is uncertain.

3. *Treatment by diet.* The association of defective diets with intestinal disease is well known in tropical countries. Deficient diet is a very important predisposing factor in such conditions. Particular attention is directed to the vitamin B complex by some experimental work by McCarrison in 1921, and recent experiments by Wills which have shown that a deficiency of this vitamin may cause colitis. Hare used vitamin A and B products in large doses in the treatment of acute and chronic cases without satisfactory results. Ill-balanced diet cannot always be regarded as the cause, as the condition can occur in persons having adequate dietary.

Though diet deficiencies and colitis cannot be placed in the relation of cause and effect, it is important to regulate diet in the treatment of the patient. During the first acute attack a limited diet with fluids and soft solids, such as are chiefly absorbed from the small intestine, is given. Milk alone is generally not acceptable, and a large bulk of fluid increases the diarrhoea. Later, with improvement of the condition, the diet is increased but food is still given in small amounts at short intervals. Chronic patients should not be starved. They as a rule improve with generous and well-balanced diet. The diet should contain plenty of protein, *viz.*, meat, fish, eggs, milk and cheese; plenty of butter, fat, fruits and green vegetables. Carbohydrates are to be taken in moderation. In addition, special vitamin preparations are ordered for these chronic cases, *viz.*, marmite or bemax for vitamin B complex and halibut-liver oil or cod-liver oil for A and D vitamins. Liver therapy is usually of no value unless there is marked macrocytic type of anaemia.

Anaemia with a low colour index is a fairly common complication of colitis. Iron in large doses given in chronic colitis with hypochromic anaemia is of striking benefit.

Spasms of colicky pain frequently occur in colitis. Injections of atropine are useful in relieving the acute condition, atropine by mouth is given to chronic or convalescent cases. Although atropine relieves the colic it does not lessen the diarrhoea of the acute attack. There is really no satisfactory means of controlling diarrhoea and it is doubtful whether kaolin and bismuth have any beneficial effect.

Constipation is another result, which is often of spastic type. Both aperients and enemata often fail to give relief and are likely to increase the irritability of the muscle, while antispasmodic drugs relax the bowel and may permit the passage of normal stools. Liquid paraffin is very useful in such cases. (*Pro. Roy. Soc. Med.*, Nov., 1935).

ARTERIOSCLEROSIS

Arterial lesions which resemble those of human arteriosclerosis can be produced in rabbits by the administration of diets containing considerable quantities of cholesterol. It is concluded that the presence of considerable quantities of cholesterol in the diet with a resulting elevation of the level of cholesterol and other lipoids in the blood is essential to the development of the typical arterial lesions in rabbits. It is shown, however, that hypercholesteremia alone cannot be regarded as the cause of the lesions in the arteries. There are preliminary local alterations in the walls of the arteries which precede the precipitation of lipoids. Evidence is advanced to show that these preliminary changes are due to some form of injury to the arteries attendant on the experimental procedure of cholesterol feeding. It is concluded that the occurrence of local changes in the arterial walls, due in all probability to injury of some kind, is the primary event in the development of the lesions of

experimental cholesterol arteriosclerosis, an event which is followed subsequently by the precipitation of lipoids in the injured areas. A comparison is drawn between the lesions of experimental cholesterol arteriosclerosis and those of human arteriosclerosis. It is demonstrated that the two diseases are not identical, and that there are a number of important differences between them. Hypercholesteremia is not found with any regularity in association with human arteriosclerosis. It seems highly probable that arteriosclerosis in man can and usually does develop without deviation of the cholesterol content of the blood beyond the normal limits of variation (*Archives of Pathology*, 1935, Vol. 20, p. 293).

YAWS AND SYPHILIS

Acute yaws (p. 655) is comparatively easy to manage by treatment, though what the final results of the treatment will be cannot yet be determined. The primary lesions of yaws and of syphilis differ decidedly in their histological features. The secondary lesions of acute florid yaws differ decidedly in their gross appearance from most secondary eruptions of syphilis, though syphilis rarely causes lesions like those of yaws, and yaws is said sometimes to cause eruptions like those of syphilis. Histologically, typical lesions of yaws are characterised by the presence of spirochaetes, chiefly among the epithelial cells, by marked proliferation of the epithelium downward, by the large number of leukocytes that penetrate the epidermis and by the slight amount of involvement of blood vessels. Thus, the papules of yaws differ from most syphilitic lesions, but occasionally condyloma and some of the cutaneous lesions of syphilis may give similar pictures. Late ulcers of yaws and those of syphilis are so much alike that a diagnosis between them is frequently impossible. It has sometimes been noted that in certain tropical regions similar conditions were likely to be called syphilis in the city and yaws in the country. As to involvement of bone, it must be admitted that roentgenograms show that the bones are often affected in yaws and that the pictures are often like those seen in cases of syphilis. Both clinical and experimental work indicate that an attack of yaws confers considerable immunity against a second infection. Also, clinical observations and laboratory experiments suggest that a certain amount of cross immunity between yaws and syphilis may be produced, but the statements are somewhat conflicting. Opinions on the relationship of yaws to syphilis differ widely. Yaws has been called syphilis of the tropics and stone-age syphilis; syphilis and yaws have been called brother and sister as well as twins. Castellani regarded them as wholly distinct infections, like tuberculosis and leprosy. Apparently no one has recorded having actually witnessed the transformation of yaws to syphilis or of syphilis to yaws in man. The evidence that is available gives the impression that the spirochaete of either yaws or syphilis has

undergone a functional but not a morphological mutation in some human host, giving rise to the other infection, and that the resemblances between the two infections indicate that the new infection has evolved from the older one in comparatively recent times. (*Archives of Pathology*, 1935. Vol. 20, p. 626).

STAPHYLOCOCCAL INFECTION OF JEJUNUM AND ILEUM

Staphylococcal infections of the small intestine occur which give rise to septicæmia and prove fatal within approximately thirty-six hours from the onset of symptoms. The early symptoms are like those of staphylococcal food poisoning, and consist of nausea, vomiting, diarrhoea and prostration. Later, with septicæmia and circulatory failure, coma and various other neurological signs appear.

The autopsy shows widespread lesions of unusual character in the jejunum and upper portion of the ileum. The intestinal contents are blood stained, and include long casts of the mucosa which are composed of necrotic fragments of intestinal villi, fibrinopurulent exudate, and staphylococci in large numbers. The microscopical sections show diffuse superficial necrosis and acute inflammation of the mucosa of the jejunum and portion of the ileum affected, associated with numerous staphylococci in the inflamed tissues. Thrombi in small vessels are found in a number of organs, and are most numerous in the jejunum, ileum and liver. There are focal necroses in the liver, spleen and bone-marrow, and small hæmorrhages, not associated with thrombi in blood vessels, are scattered in the brain and meninges. (*Bull. John Hopkins Hosp.* 1935, Vol. 57, p. 289).

WEIL'S DISEASE

Weil's disease seems to be one of those conditions fated to play an ever larger part in medicine and public health. It has been shown that: (1) the Weil strain of *Leptospira* is the same the world over; (2) at least 10 per cent. of wild rats in the United States harbour and excrete virulent organisms; (3) occupational exposure exists (most of the 12 reported cases occurred in persons working at certain trades); (4) spirochetes have been found to thrive in water in many places and (5) sporadic cases of Weil's disease (clinically and pathologically identical with the classic European variety) continue to be reported at intervals. (*Archives of Pathology*, 1935, Vol. 20, p. 478).

FEVERS OF THE TYPHUS GROUP IN INDIA (p. 375)

Boyd has analysed one hundred and ten cases of fever of the typhus group according to their serological reactions with *B. proteus* XX, X2 and X19, and according to their clinical characters. A definite XX group is described corresponding closely to Malayan "scrub" typhus. It is suggested that there may be two other types of typhus found in

India, one having as the main antigen of its virus an unknown strain of proteus, and resembling in this and in other features the Rocky Mountain fever, the second having X19 as the main antigen of its virus and resembling endemic typhus. But it is possible that these two types may in reality be but one.

In other countries (Japan and Malaya) the vector of the fever in which XK is the main antigen of the virus is known to be a mite. This is obviously a possibility in the Indian XK cases, but so far there is no evidence of any kind in support of this hypothesis. From a comparison of the clinical details of the cases, there appears little doubt that some of the cases correspond to what have figured from time to time in the literature of the disease as "Indian Tick Typhus." Whether or not the tick is the vector, or the only vector of this disease remains an open question. There exists at present no definite scientific proof on this point. The absence of any history or evidence of tick bite in the present series of closely questioned and closely examined cases is a finding which cannot lightly be disregarded; in only one is there any suggestion of tick bite, where a papule with a necrotic centre was observed; no ticks were seen; there was no associated adenitis. It is of interest to note that a definite history of tick-bite is a most inconstant feature in most cases which have been reported in the literature. Until the differential diagnosis of these fevers is more clearly established, the diagnosis "Indian Tick Typhus" should be shelved. There is at present no scientific justification for applying it to any one of the types of the disease which have been described. (*Jour. Royal Army Med. Corps.*, 1935, Vol. 65).

DIABETES MELLITUS (p. 1043)

A summary of the more important and original conclusions arrived at by the Diabetes Clinic of the Ministry of Pensions is as follows:— (1) Several cases of diabetes were found to supervene on certain specific pancreatic lesions, particularly acute pancreatitis many years previously. (2) The connection of diabetes mellitus with functional nervous diseases hyperthyroidism and consequent hyperadrenalinæmia, having been considered, the conclusion is offered that nervous shock and prolonged mental stress and strain are frequent causes of diabetes, particularly amongst war pensioners. (3) The small incidence of a family history and of obese subjects in the series is explained by the dietetic habits and type of life enforced upon most of the patients during the War period. (4) The relationship of renal glycosuria to diabetes mellitus is that renal glycosuria frequently represents a residual condition after a mild case of diabetes has been cured. The absence of any senile cases of renal glycosuria is explained on the assumption that the renal threshold rises as arterio-sclerotic changes set in with advancing years, and that the condition frequently undergoes a spontaneous cure. There is no evidence in these patients that any case of renal glycosuria

afterwards developed diabetes. (5) Three conditions are considered: (a) Diabetes mellitus, (b) "para-diabetes" or hyperglycaemic glycosuria, (c) renal glycosuria. To distinguish between these the use of a three-day blood-sugar tolerance test is advised. This is really a pancreatic exercise tolerance test. (6) The former very low carbohydrate high fat diets, the legacy of the pre-insulin period, are condemned as unsatisfactory. It is shown that carbohydrate and fat can be interchanged in a diet without greatly affecting the insulin requirements, although there are some individual variations.

Diets containing a high carbohydrate allowance with restricted fats are shown to be the most satisfactory for general use. The restriction of fats may not be agreeable to the patient, but the discomfort is not so great as the extreme restriction of carbohydrate. In practice it was found that the old diets were not kept to by the patients and apart from the distaste were expensive. The present diets are more satisfactory and kept to more readily. (7) In cases which show fasting hyperglycaemia on insulin treatment the giving of a small part of the morning dose of insulin at waking is shown to result in all cases in satisfactory blood-sugar control. (8) In many cases receiving insulin treatment the renal threshold tends to fall as an improvement in tolerance occurs. (9) As regards insulin treatment every case of true diabetes, however mild, should be given insulin, at least for a short course of treatment. They consider that it may improve the tolerance, and possibly may effect a cure. The patient's general condition is improved; in other words it acts as an excellent tonic. It also prepares the patient to deal with an intercurrent infection should it arise. In the case of a febrile condition such as pneumonia, or a septic condition insulin is well tolerated and should be given in increased quantities. It is necessary to give carbohydrate, possibly as glucose, at the same time. In cases of tuberculosis the prognosis is improved by the high carbohydrate diet with large doses of insulin.

The method of instituting treatment advised is that the patient, having been placed on the appropriate diet selected for final use, insulin is administered in two daily doses, increasing the dose at intervals of three days, until the blood sugars, taken several times throughout the day, are within normal limits. To arrive at the appropriate diet the calories sufficient for the patient's needs must be calculated, and is considered best that the subject should be maintained slightly under rather than above the normal weight. In emaciated cases high carbohydrate diets are to be given at first. High fat diets with restriction of carbohydrates tend to ketosis and death from diabetic coma.

Most mild or moderate cases can be well controlled by two insulin doses, generally given twenty minutes before breakfast and the principal evening meal. In more severe cases where there is difficulty arising from a high fasting value of the blood-sugar, the divided morning insulin dose has resulted in great success. It is shown that

in nearly every case perfect control of the blood-sugar was obtained with a smaller insulin dose. (*Jour. Trop. Med. and Hyg.* 1935, Vol. 38).

CHORIOMENINGITIS

Acute Lymphocytic Choriomeningitis

There is evidence to show that some if not all such cases represent a disease entity due to a filtrable virus described by Dickens and Armstrong. The clinical picture of the disease is that of an infection of the upper respiratory tract, followed by meningeal symptoms which are ushered in by sudden onset with headache, nausea or vomiting, rise in temperature to 100°F., stiff neck, and usually a positive Kernig sign. There is no evidence of nerve involvement and, other than noted above, the neurological examination is negative. The disease runs a benign course for about 10 days to 2 weeks. The temperature declines by lysis and recovery is complete without residuals of any kind. Four patients who have been followed for more than 3 years remained entirely well.

The cerebrospinal fluid is under slightly increased pressure and is clear or at the most slightly hazy. The cellular response is almost entirely lymphocytic—rarely do we find as many as 10 per cent. polymorphonuclear leucocytes in the fluid. The number of cells may range anywhere from 50 to 2,000, according to the severity of the attack. The chemistry of the cerebrospinal fluid is important in that the sugar, chlorides, and urea content will be found within normal range. The Kahn or Wassermann is negative and the colloidal gold curve will be in the meningitic zone and of low colour change. No organism or clot can be demonstrated. Drainage of a few cubic centimetres of cerebrospinal fluid will usually relieve the headache and nausea, and quieten the patient. The white blood cell count may show a slight increase up to 9,000 or 11,000 with a fairly normal differential percentage. The fact that the cerebrospinal fluid shows no tendency to clot and that the sugar and especially the chlorides remain within normal limits are most important diagnostic points definitely against tuberculous meningitis, with which the disease is at first often confused. The fact that no muscle weakness, or definite neurological signs are found helps to rule out encephalitis (of all types) and acute anterior poliomyelitis.

The virus of Armstrong produces a symptom-complex in monkeys similar to the above. The blood serum of patients recovered from the disease protects animals from the virus of Armstrong (National Institute of Health strain). This disease occurs sporadically in man, and has been transferred experimentally to animals. Traub has isolated a virus from white mice and Rivers and Scott have isolated a virus from human patients which are serologically identical with the National Institute of Health strain of the Armstrong virus. (*United States Naval Medical Bulletin*, 1935, Vol. 39).

BACTERIAL FLORA OF THE NORMAL BODY (p. 760)

The bacteria are able to live in the body or its cavities for long periods of time without causing demonstrable harm and must therefore be considered normal inhabitants of the body. It is customary for the secretions from the mouth, the vagina, and the urinary bladder, to contain a few pus cells, or at least cells which under other circumstances would be called pus cells. Likewise, it is evident that there are almost constantly signs of inflammation in the mouth and in other body cavities. So long, however, as there are no symptoms which would ordinarily be noticed, we are accustomed to call a given organ normal. Cultures made under anaerobic conditions yield one flora, while those grown in air show another. The time of the year, the geographical location, the food habits, the hygienic habits, and various other individual differences of the host play their parts in determining the flora to be observed. In describing the various organisms which are found in normal bodies it is necessary to distinguish between those that are practically always found, those that are frequently found, and those that are occasionally present. In the first group is *Staphylococcus albus*, which is always found in the skin of the human being. Likewise, *Escherichia coli* seems to be a normal inhabitant of the bowel of every human being wherever he may be found. *Streptococcus viridans* is said always to be found in the nasopharynx, and *Lactobacillus vaginatis* is almost always found in the human vagina, provided middle-some douching has not altered the normal habitat. In the second group are those organisms which are so frequently present that they elicit no surprise when they are found. Of these there are a great number, but we are, of course, mostly interested in those which are capable of acting as pathogens—staphylococcus, pneumococcus, streptococcus, and a number of others which need not be mentioned in detail.

In the last group we place those organisms which are occasionally present. Typhoid 'carriers' may be perfectly well and yet carry virulent typhoid germs. Likewise, there are those who harbour the meningococcus, the gonococcus, the organisms of syphilis, the diphtheria bacillus, the germs of tetanus, of gas gangrene, and probably a great many others, yet give no outward signs of disease.

FLORA OF THE NORMAL ALIMENTARY TRACT. *Mouth and pharynx.* Many bacteria live in the mouth and throat. Moisture and food are abundant. Contrary to the usual belief, saliva has but slight bactericidal effect. Dogs and animals lick their wounds and commonly experience rapid healing, but this is more likely due to the fact that the wound is kept clean by this method than to the theory that the saliva inhibits the bacterial growth. There is usually some degree of catarrhal inflammation of the mucous membrane of the mouth, but wounds of the mouth usually heal rapidly. This is largely due to the unusually rich blood supply. It is impossible to sterilize the mouth cavity, and any

attempt to do so is certain to do more harm to the mucous membrane than to the germs. If the mucous membrane is injured the body's protection against germs is weakened and bacterial invasion is more likely to take place. The organisms found in the mouth are of many kinds:—*Staphylococcus albus* is often there; and occasionally *Staphylococcus aureus* can be found. *Streptococcus viridans* is nearly always present; *Streptococcus hemolyticus* and non-hemolyticus may be present without causing disease, and are, indeed, fairly common. *Pneumococcus* is present in a large percentage of mouths, especially during the winter and spring months. The pneumococci found usually belong to Type IV, which is the least pathogenic. The other types are rarely found in normal mouths except when the person is in contact with a case of pneumonia of the same type. *Gaffkya tetragena* is rather common. Of the genus *Neisseria* several species are rather commonly found, particularly *Neisseria catarrhalis*, which has been accused of causing a catarrhal inflammation of the mucous membrane of the nose, throat, and sinuses. It is probably of slight importance, but cannot be classed as being entirely harmless. Other Gram negative diplococci are found and make it hard to be sure, when the presence of meningococcus is reported, that the organism of Weichselbaum is really present. The true meningococcus is not infrequently found in the throats of normal individuals. *Corynebacterium diphtheriae* and *C. pseudodiphtheriae* may be present in the normal throat. The fusiform bacillus and the spirillum of Vincent are present in a large percentage of mouths. Some authorities are finding them in nearly all mouths, but this seems an exaggeration. Several species of *Treponema* are sometimes found and may be mistaken for *Treponema pallidum* in a dark field examination. *Proteus vulgaris*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, and a number of other Gram-negative bacilli are often found. Chain-forming Gram-positive bacilli are common; also a great many large saprophytes, yeast cells, and occasionally *Leptothrix* and *Streptothrix*. Sarcinae are common.

Oesophagus. The flora of the oesophagus is essentially the same as that of the mouth and the pharynx.

Stomach. The acid of the gastric juice usually kills all bacterial growth. As a result, food commonly leaves the stomach in a sterile condition. Undigested food, of course, contains many bacteria, and some may pass into the duodenum in the centre of compact masses of food. One of the most important functions of the gastric juice is that of disinfection of the food. With normal gastric digestion there is much less danger of dysentery, typhoid fever, cholera, food infection, and related conditions. Persons with weak gastric digestions, will suffer from fermentation of the food in the stomach, causing discomfort, foul eructations, and indigestion. Many people cannot drink sweet milk because of the large amount of buffer substance in the milk, which neutralizes the gastric juice, allowing the bacteria in the milk to ferment

the lactose with gas. Most of these people can, however, drink butter-milk, because in this case the lactic acid reinforces the gastric juice and the lactose having already been fermented cannot produce gas. Patients with cancer of the stomach commonly have a very low acidity. The Oppler-Boas bacillus is often found in such gastric juice and has been supposed to be the cause of the cancer. This is not the case, since the Oppler-Boas bacillus is one of the non-pathogenic *Lactobacillus* species and simply lives in the stomach as a saprophyte. It is largely responsible for the organic acid commonly found in the gastric contents of persons with carcinoma of the stomach.

Intestine. The contents of the normal duodenum are usually nearly sterile, but the bacteria rapidly increase as the lower levels are reached. It is commonly stated that about one-third of the faeces are composed of the bodies of dead and living bacteria. The commonest organism is *Escherichia coli* (or possibly *Esch. communior*). There has been much discussion as to whether we should regard this organism as a friend, an enemy, or a harmless saprophyte. The noted pathologist Adami traced a great deal of trouble to the colon bacilli. He thought that the portal circulation took them up in large numbers, that the liver had the important task of destroying them, and that a chronic state of intoxication resulted. The Russian bacteriologist, Metchnikoff, believed that they were the cause of old age and attempted to supplant them with *Lactobacillus bulgaricus*. The whole theory of lactic acid therapy is based upon the assumption that the usual flora of the bowel is harmful. Other authorities regard the colon bacilli as being of some benefit. They point out that they may aid in the digestion of certain products, though this seems rather far fetched for the reason that the things that they will digest (sugars) are easily broken down by the intestinal juices. They say that colon bacilli tend to inhibit the growth of worse germs and this is quite plausible. Others think they are a harmless organism, except in a few cases when they get into other organs or may cause a colitis in debilitated individuals. The bacterial flora of the bowel varies with age and diet. At the time of birth the bowel contents are sterile. From the first to the third day, however, there is a period of "adventitious bacterial infection," and after this time the bowel will be heavily contaminated for the remainder of life. The flora of the breast-fed baby is usually characterised by the presence of *Lactobacillus bifidus* in large numbers. The stools of such a child are inoffensive in odour. Other organisms present are *Aerobacter aerogenes*, *Streptococcus lacticus*, *Escherichia coli*, *Escherichia communior*, *Lactobacillus acidophilus*, etc., several of which are anaerobic and proteolytic. In adult life there is a relative increase in the number of the members of the coli group, and a corresponding decrease in the sour milk type of organism. The colon comes to harbour a great number of the organisms belonging to the genus *Clostridium*. *Clostridium welchii* is often found in the normal

colon, and may, as in cases of pernicious anæmia, ascend to much higher levels. It has, indeed, been accused of being the cause of this disease. The more likely explanation is that it is allowed to ascend in the bowel for the reason that the bowel does not have a normal function because of the atrophy of mucosa so characteristically seen in this disease. The presence of the Welch bacillus is, then, probably a result rather than a cause of the condition. This organism can cause a marked diarrhoea with much gas formation. *Bacillus mesentericus* is a common inhabitant. In many respects it resembles *Bacillus subtilis* and produces an active proteolytic ferment, making it important in the putrefactive processes taking place in the bowel. *Clostridium putrificum* (Beinstock) is considered to be a normal inhabitant of the faeces and is active in putrefaction. A great many other organisms of less importance are found regularly and still others occasionally in the perfectly normal intestine. With a special milk diet the faecal flora tends to change toward the acidophilic forms. Two factors determine the degree of such transformation : (1) The original presence of appreciable numbers of *Lactobacillus acidophilus* in the lower part of the digestive tract. (2) The stability of the flora that were already established when the special feeding was begun: A diet high in carbohydrate tends to simplify the flora in favour of the acidophilic organisms, while a meat diet tends to favour the colonic flora and to induce putrefaction. In other words, a carbohydrate diet tends to establish the fermentative organisms, while a high meat protein diet tends to cause the putrefactive organisms to flourish.

FLORA OF THE RESPIRATORY TRACT. *Nasal cavity.* It is one of the functions of the nasal cavity to remove dust and germs from the inspired air so that the lower levels of the tract may be protected from such contamination. As the air enters the nostril it first encounters the vibrissae, or hairs, which grow in the vestibule of the nasal cavity. These hairs are more or less moist and catch a great deal of dirt, as every one knows who has worked or lived in dusty places. As the air passes on into the nose it comes in contact with the moist surfaces of the mucous membranes and a large part of the dust remaining is left in the slimy covering of those membranes. The arrangement of the folds of mucous membrane over the turbinates is such that the air is swirled about so that every particle of dust is likely to come into contact with a moist surface. Once the germs find themselves caught in the mucous secretion they may be blown out of the nose, may drain into the throat to be swallowed and destroyed in the stomach, or they may be expectorated. There is likewise some method, by no means understood, by which they are destroyed by the mucous membrane itself. Doubtless phagocytosis plays an important role in this respect, though there are apparently other means at the disposal of the membrane.

As might be expected, a great variety of organisms are found in the nose. Probably the most common ones of interest to physicians are *Staphylococcus albus*, *Neisseria catarrhalis*, *Streptococcus viridans*, and certain diphtheroids. A variety of cocci and rather frequently members of the colon group and the Friedlander group are commonly found. The fact that these organisms are found in noses that are normal indicates that while the nasal secretions may not be definitely germicidal, they are by no means favourable for growth and development in such a way as to cause disease. It is likely that the increased susceptibility to cold which is rather characteristic of civilized man is due to the fact that he mostly lives indoors, where the air is likely to be dry, dusty, and overheated, thereby producing excessive dryness of the membranes of the nasal cavity and reducing resistance to bacterial invasion. Increased opportunity for contacts with other persons suffering from colds is also a big factor. Hypertrophy of the adenoid tissue of the throat and nasopharynx is doubtless a response to the excessive load thrown upon the lymphatics by reason of the inability of the mucous membrane to perform its full function when excessively dry and heavily contaminated by dust and germs.

Accessory sinuses. The strictly normal sinus is probably always or nearly always sterile. Cultures made upon fresh human cadavers dead of various causes and without sinus symptoms usually give no growth, or, in a few instances, non-virulent strains of *Staphylococcus albus*. When bacteria have been injected into the sinuses of normal dogs they have usually remained viable for only a few hours. The drainage from the sinuses is such that this result is to be expected, provided there is no source of continued reinfection. In recent years there has been much attention given to the apparent increase of sinusitis. It sometimes seems that, in certain regions at least, there are no really healthy sinuses. *Staphylococcus albus* and *aureus*, various Gram-negative diplococci, and streptococci are the more common offenders. In not a few of these cases the sinus seems to be normal sometimes for weeks or months at a time, but in all probability the organisms are still there in latent form.

Bronchial tree. The ciliated epithelium of the trachea, bronchi and the branches of the bronchial tree is constantly sweeping the mucus upward so that it may be expectorated or swallowed. In this way large quantities of dust are removed, as every one knows who has coughed up dark material after having been exposed to dust or coal smoke. As cultures are taken deeper and deeper in the bronchial tree the number of organisms obtained becomes less and less until it is found that the really healthy parenchyma of the lung is sterile or practically so. Sometimes after deep and labored breathing with the mouth open germs succeed in getting into the depths of the

lungs, but in quiet breathing this rarely happens except when there is a heavy infection of the upper respiratory tract or the germs are carried to the lungs by the blood stream.

FLORA OF THE GENITO-URINARY TRACT. *Urethra.* The short female urethra is frequently sterile but also often is contaminated with *Staphylococcus albus* and colonic organisms. The male urethra usually shows the presence of these two types of organisms and in addition often furnishes a habitat for non-pathogenic diphtheroids. *Mycobacterium smegmatis* is commonly found in the folds under the male foreskin and also in the creases between the various members of the external female genitalia. It bears a close resemblance to the tubercle bacillus and may easily be confused with it unless its presence is kept in mind. The deeper parts of the male genito-urinary system are sterile when free from disease. Occasionally organisms are found in the urinary bladder when there seems to be no evidence of infection, but it is doubtful if they can be regarded as being normal or harmless inhabitants.

Vulva and vagina. On the vulva, as might be expected streptococci, staphylococci, *Escherichia coli*, *Corynebacterium pseudodiphtheriæ*, and many saprophytes are to be found. During the later weeks of pregnancy streptococci and staphylococci are found in the vaginas of 40 to 75 per cent. of healthy women. Such being the case, it is easy to see that it is not necessary to suppose that puerperal fever can take place only when the germ is carried to the parturient woman. We should remember, however that the germs which are commonly present in the vagina of a particular woman are far less dangerous to her than those which are brought from another case to a woman who has had comparatively little contact with these germs. In other words, the woman is more or less immune to the germs which she carries herself.

The classic studies of Doderlein upon the bacterial flora of the vaginal secretions are important. He distinguishes two forms of vaginal secretion: (1) Normal, which is white (like curdled milk), acid, contains no mucus, is small in amount, and (2) pathologic, which is thick, yellowish or greenish mucus, sometimes foamy, usually alkaline, but not necessarily so, and contains numerous pathogenic and non-pathogenic micro-organisms. The normal vaginal secretion usually contains only *Lactobacillus vaginalis* (Doderlein's bacillus) a harmless organism. The *Lactobacillus vaginalis* produces large amounts of lactic acid which rather effectively prevents the growth of the other organisms. This germ must be regarded as the normal inhabitant of the vagina, and its presence is undoubtedly beneficial. Because of the fact that this germ causes odours which are objectionable for æsthetic reasons, antiseptic alkaline douches have been much used. In this case the æsthetic ideal and the hygienic ideal are opposed. The removal of Doderlein's bacillus and the neutralization of the acid secretions favours

the development of bacterial flora which are capable of causing irritation and infection. There is of course, comparatively little danger of this except in the few weeks preceding obstetrical delivery. At such times douches are definitely contraindicated.

It is not unlikely that the reason for the great number of cases of puerperal fever in women delivered under the most careful attempts at asepsis is due to the fact that many women who have habitually used douches have not had the normal experience with germs which is necessary for the development of an immunity to them. Such women are in much danger if an exogenous germ is introduced.

Uterus. While the vulva and the vagina are usually contaminated rather considerably, the uterus is normally sterile except for the lower third of the cervix. There is a mucus plug that closes the mouth of the womb and prevents bacteria from entering. Under certain conditions bacteria live in the contents of the uterus in the later months of pregnancy, but do not reach the child (the germ of syphilis can pass from the mother to the child, as can filtrable viruses—and possibly other germs, very rarely). The greatest care must be taken when an instrument or the hand is to be introduced into the gravid, the non-gravid, or the parturient uterus.

When there has been a considerable laceration of the cervix as a result of childbirth, bacteria invade further into the uterus. Under certain circumstances organisms can enter the uterus and cause endometritis, but the uterus is no longer a normal organ in that case. The gonococcus can traverse the cavity of the womb and cause serious infection in the fallopian tubes and in the peritoneal cavity, but rarely causes much trouble in the uterus itself.

FLORA OF THE NORMAL TISSUES. It has often been supposed that the tissues themselves are commonly sterile except when definitely infected. This is by no means true. It is easy to show by anaerobic cultures that the muscles, the liver, and probably other organs harbour members of the Clostridium group when apparently perfectly healthy. Lymph nodes frequently show the presence of living organisms which, in all probability, they are in the act of destroying. The liver has been shown to receive considerable numbers of organisms which have passed through the intestinal wall into the portal vein and thence to the liver. It is doubtless an important function of the cells lining the sinusoids of the liver to pick up these organisms and destroy them before they go further. Diphtheroid organisms can be isolated from a number of organs of the body. They have been found a number of times in pathogenic lesions which are probably non-infectious and have erroneously been supposed to be the cause of Hodgkin's disease, sarcomata, and various granulomatous conditions; when, as a matter of fact, they were probably merely harmless parasites which had nothing to do with the disease in question.

SYMBIOSIS—MAN AND BACTERIA. It is commonly assumed that the host and the parasitic bacterium are each trying to kill the other. Each is merely trying to preserve itself against the other and in case either should cease attacking the other a condition which is essentially symbiosis is likely to be set up. As soon as the acute ravages of gonorrhoea are overcome, the body is rather content to allow the organism to lie latent in the tissues. Many organisms which cause disease—or indeed, most of them—may thus lie latent for weeks, months or years, causing little or no harm but able to seize an opportunity further to invade the tissues or to spread even to other individuals. This is an important immunological fact that has too often been overlooked. Inasmuch as we rarely make bacteriological examinations on persons except when they are in the grip of a definite infection, this principle has often been missed or inadequately appreciated. We are constantly living in symbiosis with many kinds of bacteria and billions of individuals of the various species. Indeed clinical healing in a large percentage of cases is merely an armed truce which upon slight provocation may become active warfare. A large percentage of lesions—abscesses, tubercles, gummata, etc.—are merely localizations of the conflict when the resources of the body have been more or less successful in interning the organism and compelling it to restrict its activity, though it is by no means dead.

At the same time that the patient is becoming immune to the attack of the germ, the germ is also in many instances becoming immune to the attack of the body. This "reciprocal immunity" enables each to live in the presence of the other, or in other words, to establish a condition of symbiosis. An example of this is seen when children are immunized against diphtheria by being given toxoid. The immunity produced is an antitoxic immunity directed against the toxin rather than against the germ itself. In such case the individual is protected against the clinical form of the disease but not against the carrier condition. There is reason to believe that the number of carriers will increase if immunization continues to be practiced, though clinical diphtheria may become quite rare.

This principle may be the explanation of the apparent fact that many diseases seem to be decreasing in virulence though they still produce much morbidity. Inasmuch as man has never been able, by artificial means, to bring about the total extinction of any biological species the attempts to do so in the case of various disease germs may be quite impracticable. It is not unlikely that we might be more successful if we should seek rather to gain a truce and accept the principle of "live and let live". The physician must give consideration to the general biology of symbiosis in his study of the forces by which his patient achieves victory, accepts balance, or submits to defeat and death as a result of bacterial invasion. (*Text-book of Bacteriology*—T. B. Rice).

BACTERIOLOGY OF URINE

Suggestions to the bacteriologist and clinician in deciding what to look for in a given specimen of urine.

MYCOBACTERIUM TUBERCULOSIS. Tuberculosis of the kidneys and bladder is not particularly rare. When it is at all possible specimens to be examined should always be collected through a catheter for the reason that they may otherwise be contaminated by the smegma bacillus which is nearly always present on the external genitalia. This organism is acid fast and very similar to the tubercle bacillus in many respects. If tuberculosis of the kidney is suspected the ureters should be catheterized through a cystoscope and the urine from the two kidneys kept separate. Direct microscopic examination of the urine will rarely be successful. The urine should be sedimented in the centrifuge, the clear urine poured off, and salt solution poured on, shaken and again sedimented; the sediment is then injected into the peritoneum of a guinea pig. In case the smegma bacillus is present, guinea-pig inoculation will rule it out since it is not pathogenic.

STAPHYLOCOCCUS. It is often the cause of cystitis and may be easily found if present in the urine. A smear of the sediment will reveal numerous pus cells and the organisms themselves. Culture on ordinary culture media will easily establish the identity of the organism.

STREPTOCOCCUS PYOGENES. It may be present in the urine, usually coming from the kidney or the kidney pelvis, but occasionally coming from the bladder itself. Catheters in the ureters will decide the source of the infection. Streptococci in the sediment will call for enriched culture media and more careful methods of culture. If autogenous vaccines are to be made from the streptococci great care must be exercised in the giving of them as they are likely to cause a focal irritation of the kidney with swelling and suppression of the urine. Very small doses should be given until one is sure that the patient is not excessively sensitive.

ESCHERICHIA COLI. It is rather frequently found in the urine of cases of cystitis. Much care should be taken in the use of a catheter in patients with large prostates and residual urine that this organism is not introduced. Infection of the bladder of debilitated patients with this organism may be a serious matter. The colon bacillus is, of course, easily cultured and identified. Patients with spinal cord injuries are very liable to cystitis of catheter origin.

EBERTHLLA TYPHI. The urine of typhoid fever patients carries the germ in a large percentage of cases. For this reason the urine should not be infected with the feces. The fact that the germ is in the urine may occasionally be used for diagnostic purposes but rarely so. Urine "carriers" are very dangerous.

PROTEUS VULGARIS. This organism is rather easily separated from the last two by the fact that it rapidly liquefies gelatin medium. Otherwise it is much like the colon bacillus for all practical purposes.

NEISSERIA GONORRHOEA. The gonococcus is occasionally found in the urine but the fact is of no practical significance. The organism has merely been washed out of the urethra in the act of urination and its presence does not mean that the bladder is involved in the specific inflammatory process.

Several other organisms have been occasionally found in the urine, as *Borrelia recurrentis* (relapsing fever) and the organism of Weils disease (epidemic jaundice), etc., but these are, of course, very rare and need not be considered in a manual of this sort.

COLLECTION OF SAMPLES

SPUTUM. If sputum is to be cultured it must be received into a sterile container and without disinfectant of any sort. It is usually well to rinse the mouth and throat with a cleansing—but not disinfectant—gargle and mouth wash. Boiled or sterile water or salt solution is good for this purpose. Effort should be made to get the sputum from the part affected—lungs, throat, posterior nasopharynx, etc,—with the least possible contamination from the saliva of the mouth. The sputum should be taken at once to the laboratory and kept in a cool place.

If the sputum is to be examined for acid-fast organisms but is not to be cultured or injected into an animal, it should be taken in a 5 per cent. phenol solution in equal volume with the sputum. Morning sputum is more likely to have the germs.

THROAT SWABS. For suspected diphtheria use no gargle of any sort. Depress the tongue and inspect the throat carefully. The physician should be careful to avoid causing the patient to cough or sneeze into his face. It may be well to wear a mask. The tongue depressor used should be perfectly clean and the swab should be carefully taken and planted on the culture medium. Other swabs are taken in much the same manner from the throat and planted upon appropriate media. In suspected meningococcus cases or carriers the culture is taken from the nasopharynx through a glass tube to avoid contamination with other secretions. The swab is then immediately planted upon special warmed medium in a plate poured but a few minutes before. It is usually better to have the suspected 'carrier' come to the laboratory than for the bacteriologist himself to go to the bedside of the patient.

Direct smears. When stained smears rather than cultures are to be made, the material should be evenly and thinly spread upon a clean glass slide that has been properly labelled. The film should be allowed to dry thoroughly in air. A number of germs will remain infectious when the film is spread upon a slide and dried in the air.

Smears for gonococcus should be taken in such a manner as to ensure that the germ may be found (after massage of the prostate in chronic cases in the male) and that contaminating germs may be

avoided (taken from the cleaned cervix through a vaginal speculum in the chronic case in the female). At least two smears should be taken.

EXUDATES AND TRANSUDATES. These can usually be handled in much the same manner as pus or other liquids and hardly require detailed instructions.

SPINAL FLUID. Obviously the most rigid asepsis should be practised in entering the spinal canal. It is therefore easy to collect the fluid under ideal conditions from a bacteriological standpoint. When the meningococcus is sought by direct stain the stain should be made as promptly as possible. When the fluid is to be cultured it will often happen that incubation at body temperature will greatly increase the chances of culture. A clear spinal fluid suspected of containing the tubercle bacillus should be allowed to stand for several hours in the ice box and both the fluid and sediment studied. Fluids containing other organisms should be handled as would other fluids for bacteriological study.

BLOOD CULTURES. Very important is the thorough cleansing of the skin before inserting the needle. Unless scrupulous surgical technic is used there is a great danger of contamination with the staphylococci which are so commonly present on and in the skin. When a staphylococcus septicaemia is suspected extreme care will need to be taken else one cannot decide whether the organism was in the blood or on the skin. If *Staphylococcus albus* is found it is usually a contamination.

BLOOD FOR SEROLOGICAL TESTS. It need not be drawn with such care as indicated here, except that such measures as will protect the patient from infection must be observed.

TISSUES REMOVED BY BIOPSY. The area should be very carefully washed but antiseptics must be used sparingly or not at all. Rigorous asepsis must be used and the tissue received into a sterile Petri dish or wide-mouthed tube.

PUS. The manner of the collection of pus will vary according to the quantity of the same and the lesion from which it comes. If a large abscess is aspirated it is usually easiest to inject the pus directly from the syringe into a sterile culture tube with a cotton stopper. If the pus is to be sent some distance a sterile tube can be drawn out making an ampoule. The pus is injected below the constriction which is then sealed with the flame. A smaller amount of pus may well be collected in a 'Pasteur pipette'. After the capillary end is properly sealed in a flame the tube can be packed in a case and handled quite conveniently without fear of breakage or contamination. Pus from ulcers of various sorts is commonly taken on a swab and then transported in a sterile tube with a cotton stopper. An objection to this manner of taking a sample is that the pus may dry out. This is not commonly a serious matter unless considerable time must elapse.

FÆCES. It would seem too much to demand that fæces be received and handled only in sterile vessels, but it is essential at least that the

container be scrupulously clean, else there is danger that the organisms from other cases may be carried over into the specimen. A clean white enamel pail of one or two quarts capacity is probably the best container. It should have a tight lid in order that the escape of odours may be avoided. The plant should be made as soon after collection as possible and it is best to keep the material in the icebox until the examination is made. Faeces examinations are most commonly made for the typhoid and dysentery bacilli; also the stools of infants with various diarrhoeas or of adults following food infection. Examination for acid-fast bacilli is likely to be very misleading.

It is frequently best to take the material for faecal examination on a swab taken directly from the bowel through a proctoscope or sigmoidoscope. This is particularly true in ulcerative conditions—colitis, dysentery, etc.

URINE. The bacteriologist should refuse (except under very unusual conditions) to examine a urine bacteriologically unless it has been drawn through a sterile catheter into a sterile bottle with a suitable stopper. Highly significant in urine examinations are the staphylococci, the *Esch. coli*, and the tubercle bacilli. The first two of these may be introduced into the urine during the act of normal passage, and the smegma bacillus normally found about the genitalia is very likely to be confused with the tubercle bacillus. Clinicians will say that the bacteriologist should distinguish between *Mycosmegmatis* and *Mycotuberculosis*, but this is far harder to do than to insert a catheter and is much more likely to result in error. If information is desired concerning the urine from a particular kidney, ureteral catheterization should be done when practicable.

If a contaminated urine is sent to the bacteriologist and he finds organisms which did not really come from the urine the report is almost sure to be very misleading and may cause serious error. For this reason aseptic care must be taken in preparing the genitalia and inserting the sterile catheter. Never send a specimen of urine to the bacteriology laboratory unless it has been drawn through a sterile catheter into a sterile bottle with a sterile cotton stopper. In taking the specimen to the laboratory do not wet the stopper.

BACILLUS ACIDOPHILUS

The implantation of this organism in the intestine has given some remarkable results in the experience of many clinicians. The organism must be given in milk and at least 1,000 c.cm. of milk is given daily, containing 200,000,000 organisms to each c.cm. This amount of milk must be given for at least a month or six weeks. The stools should be studied and plated to see that the flora has changed before the treatment can be stopped. Under no circumstances should the tablets put up by manufacturers be used. The organism grows well in lactose

and a good preparation for treatment is for the patient to eat a good quantity of lactose daily for a week.

C. C. Bass gives the following instructions for the preparation of the milk:

Carc of stock culture. The stock culture should be kept up by frequent transplanting (preferably every day) to autoclaved milk in regular culture tubes. Relatively large amounts of inoculum must be transferred. Small pipettes drawn from glass tubing of proper size plugged with cotton before sterilizing and fitted with a rubber bulb just before using are convenient for this purpose. The outside of the pipette can be sterilized just before using by passing through a flame.

Preparation of inoculum for routine production of acidophilus milk. Bottles of skimmed milk, plugged with cotton, are sterilized in this autoclave for fifteen minutes at 15 pounds pressure. A bottle should contain as much milk as will be required to inoculate all the milk to be inoculated on a given day.

"The first bottle of inoculum is prepared by inoculating one of these bottles of milk from the stock pure culture and incubating for 24 hours or longer, until coagulation takes place. This should be broken up by shaking before using. Subsequently, the bottle of inoculum for the next day may be inoculated by pouring some of the day's inoculum into another bottle of autoclaved milk, etc.

"Preparing milk to be used in routine production of acidophilus milk: Round tincture bottles with cork stoppers having a capacity of 20 ounces ('English quarts') are most convenient for making 500 c.c. quantities. This allows extra space for shaking. They should be dry sterilized.

"Milk (skimmed or whole) should be brought to boiling temperature for a few minutes in a double boiler and poured while hot into the bottles, about 500 c.c. to the bottle. After cooling down to about 37°C. they should be inoculated.

"Inoculation: Pour 10 to 15 c.c. of inoculum into each bottle, replace the stopper, shake and put in the incubator at 37°C. for about 24 hours. Remove, shake thoroughly and place in the ice box. This is 'acidophilus milk' and is ready for use. If kept cold, it is good for at least two or three days.

Administration. Information available at present indicates that taking 1,000 c.c. or more of acidophilus milk daily results in almost complete transformation of the intestinal flora, in most individuals at least, within a period of from one to two weeks. Much smaller quantities are far less effective. Less than 500 c.c. daily probably has little transforming effect. Ideally a portion of the daily quantity should be drunk along with each meal. Unfortunately, the acidophilus flora give way to the usual mixed flora within a week or two after the acidophilus milk is discontinued." (*Methods of Treatment*. Clendenning. 1935).

DEATH OF OVUM AND PREGNANCY TEST

The value of the biologic tests for pregnancy (p. 1454) in determining intrauterine viability is not yet established. In an attempt to solve this question Bishop has summarised the results given by the test in a series of cases in which the date of foetal death could be determined clinically with some degree of certainty. The Friedman test was employed in the eleven cases of the series. In two instances the test was still positive six weeks after the death of the foetus. With these exceptions the test tended to become negative between ten and twenty-four days after intra-uterine death has taken place. The Aschheim-Zondek test, according to other reports, tends to remain positive even longer. The reason for this apparently lies in the greater sensitivity of infantile mice to pregnancy urine than that of adult rabbits. Evidence exists that the Aschheim-Zondek and Friedman tests depend primarily on the presence or absence of functional chorionic tissue rather than on the life or death of the ovum. Since, however, the main function of the placenta is to provide a means of nourishing the living embryo, it might be expected to become inactive on the death of that embryo. Practically, however, it is clear that there is no direct relation between the death of the ovum and the disappearance of gonadotropic substance from the urine. Furthermore, the time after death of the ovum at which the placenta ceases to elaborate the gonadotropic hormone seems to vary considerably in individual cases and to be determined by no mechanism so far understood. (*Jour. Amer. Med. Assoc.* 1935. Vol. 105, p. 1609).

WEIL-FELIX REACTION

The Weil-Felix reaction (p. 977) is included among the heterophile phenomena because there is now little doubt that it is brought about by a specific antigen-antibody reaction. Although the agglutination of strains of *B. proteus* X by the serum of most human beings suffering from typhus fever has been accepted as a fact since 1916, the basis of this specificity has been questionable. Until recently, most bacteriologists refused to accept the theory advanced by the original authors, who expressed their belief in the specificity of the reaction, since the agglutinins for the proteus X bacillus appeared only as the result of an antigenic stimulus, presumably supplied by the virus of typhus, but the weight of evidence to-day impels acceptance of the original view. The agglutination of *B. proteus* X occurs practically only in typhus and typhus-like fevers and not in other febrile conditions. In almost all diseases now known to have a rickettsial aetiology, agglutinins are produced for one or another serologic variety of *Bacillus proteus* OX. (*Archives of Pathology*, 1935, Vol. 49, p. 878).

X-RAYS IN DIAGNOSIS (p. 136)

It is recognized and established that X-rays are of supreme value in diagnosis not only for detection of disease but as a routine examination for the positive diagnosis of health. Every qualified practitioner should understand the extent to which they can be used in diagnosis and should be able to give an opinion on an X-ray examination. When the clinical and X-ray evidence agree the liability of error is very small but when they fail to agree both should be revised in the fuller knowledge of the facts which each has revealed.

Examination of Bones. Bones are liable to injury, inflammation, nutritional disorders, congenital defects and new growth.

INJURY. All injuries to bones should be X-rayed. The injury may be fracture, dislocation, rupture of ligaments tearing away flakes of bone, or merely bruising of the tissues. X-ray films give the fullest information and indicate the line of treatment and prognosis. In all injuries true antero-posterior and lateral views should be taken. Whenever a bone is fractured and displaced the X-ray should be available for immediate use after reduction and until a satisfactory position is obtained; thereafter the part should be X-rayed at intervals during the process of healing.

INFLAMMATIONS. Inflammations of bone produce pathological changes and these changes in structure are shown on the X-ray film. The progress of suppurative osteomyelitis, the line of demarcation of the disease stops short of destroying the shaft, the formation of the involucrum and separation of sequestra—all can be followed in accurate detail by X-ray examination. Of the chronic specific infections of bone, tuberculosis is commonest; early diagnosis is essential and the X-ray alone confirms the diagnosis and shows the extent to which the disease has spread.

DISORDERS OF NUTRITION AND CONGENITAL ANOMALIES. X-ray examination of the growing ends of bones reveals the changes peculiar to these diseases in the delicate growing bones of children, and—with the clinical evidence—establishes the diagnosis.

NEW GROWTHS. X-rays afford the only means of diagnosis in the early stages of new growth of bones—primary sarcoma and secondary carcinoma or hypernephroma. There is growing evidence that the X-ray appearances are more conclusive than even the microscopic section.

Injuries of the Skull. The value of radiography as applied to the skull is well recognised. Each patient must be studied as a separate entity and modification of the usual methods may have to be adopted to meet the vagaries of the patient's condition or complaint whether due to age or illness. Stereoscopic X-ray pictures should be a matter of routine, as many mistakes can be made from single 'flat' films that would not occur if stereoscopic films were taken. A radiograph of the skull

presents at first sight a confusing collection of linear and other shadows due to sutures, vessel grooves, depressions for Pacchionian bodies, Wormian bones and other structures. The variation of these shadows within normal limits is considerable. So is also the thickness of the skull bones. These points must be fully appreciated and considered when examining a skiagram for evidence of injury or disease.

Congenital deformities such as anencephaly and hydrocephalus can be observed in radiographs taken during the latter months of pregnancy and such knowledge may be invaluable. Later deformities such as microcephaly and oxycephaly produce well-marked appearances. In cases of meningocele the extent of the defect in the cranial bones can be observed. Hydrocephalus gives perhaps the most striking picture with the widened sutures and the dappled appearance of the thinned skull bones. The disease may affect the whole of the bones of the skull, face and jaw, and also be visible in the upper part of the spine in some of the radiographs.

INJURIES. Injuries to the skull may result in various forms of fracture. In cases of depressed fracture, these may be best demonstrated by an additional tangent view over the injured area when the extent and depth of the depressed portion of the bone will be seen. Fractures of the base may at times be difficult to demonstrate and X-ray pictures taken in several planes may be necessary before the injury is detected. Fractures of the malar bone frequently involves the maxillary antrum causing hæmorrhage into the cavity, which produces an opacity in the shadow of that sinus. Fractures of the lower jaw are usually easy to show in two or three planes. In cases where sepsis develops from a fracture or following the extraction of a septic tooth, widespread osteomyelitis sometimes occurs and spreads rapidly through the jaw producing in the radiograph a typical worm-eaten appearance of the bone with multiple sequestra of various sizes. The subsequent healing process can be followed by periodic re-examination. Foreign bodies of various nature are of course met with in different parts of the skull and nose and, provided they are sufficiently opaque radiologically, no special difficulty should occur in their localization.

NEW GROWTHS. Primary neoplasms in the cranial bones are uncommon, the ivory exostosis or osteoma being that most frequently met with. They show as a dense homogenous shadow of irregular pattern but smooth outline and varying in extent. Osteo-sarcomas are rare and produce a less homogeneous shadow and their progress is much more rapid. Tumours of the pituitary produce, as a rule, a deformity of the normal outline of the sella turcica, usually showing as an expansion in one or more directions. The posterior clinoid processes are frequently displaced and may eventually disappear and the floor of the fossa may be seen bulging down into the sphenoidal sinus. "Neoplasms of the brain rarely show in an X-ray picture without accessory methods as they

rarely contain any salts opaque to X-rays. There are a number of regions in the cranial cavity where calcified deposits are not infrequently seen and must be recognized as normal occurrences. The commonest is in the pineal gland, but in case of cerebral tumour it may be seen to be displaced in some direction and so aid in the localization of the tumour. Other regions where calcifications occur are the choroid plexus, falx cerebri, various blood vessels especially the internal carotid and parts of the dura mater. Calcification in a haematoma may occur and calcified tuberculomas, single or multiple, show as irregularly shaped shadows in sundry areas of the brain. Another form of the deposition of lime salts seen is that of the calcified haemangiomas where areas of dilated and tortuous vessels show well-marked calcification in their walls and the appearance resembles a group of worm-like deposits. Other rarer calcified deposits are seen in the cysts of *Cysticercus cellulosae* which have recently been shown to occur in the brain.

NASAL SINUSES. As a routine examination four or five views are sufficient, provided they are carried out with the necessary care. The erect posture is essential for some positions but others are more comfortably and satisfactorily obtained in the horizontal plane. The final diagnosis of the condition of a sinus must be based on the combined information obtained from all the positions. The one most commonly under observation is the maxillary antrum and practically all the pathological conditions to which it is subject can be demonstrated radiographically. A radiographic examination is the only method at present available by which a general and accurate idea of the size and condition of the sinus can be obtained. Among the common antral conditions met with are polypi which may be seen as 'cherry-like' shadows projecting from one of the walls or more commonly the floor. They vary in size and may almost fill the sinus cavity. Thickening of the lining mucosa shows as a band-like shadow round the wall of the antrum resulting in a diminution of the air space. When fluid is present, if it fills the whole cavity a homogeneous opacity is the result, but if less than full a fluid level may be demonstrated and can be shown to remain horizontal, when the head is tilted. The frontal sinuses show more anatomical variation than any of the others and range from complete absence on one or both sides to a sinus which covers a large portion of the cranial surface, there is also a corresponding variation in depth, this ranging from nothing up to one and half inches or more. Large frontal sinuses are sometimes found in cases of acromegaly. The common conditions discovered by radiographic examination are infection resulting in thickened mucosa or pus which may on occasions be seen as a fluid level. As already mentioned, chronic infection may terminate in osteomyelitis. The ethmoidal cells make an interesting technical study and they can be viewed from many angles. It is uncommon to find evidence of infection of these cells in the absence of infection of neighbouring sinuses, with

correct positioning their lesions can generally be demonstrated satisfactorily. The sphenoidal sinuses may show marked asymmetry both as regards their length and their width. They are easy to demonstrate and can be well shown in three planes. The mastoids present their own problems. The development of the process and the cells themselves vary greatly in individuals, and in the lateral view the anterior extent of the cells may be superimposed over the shadow of the sphenoidal sinus. The size of the cells also differs considerably, some being large and clear and others quite minute, and in some cases the region appears almost non-cellular. Asymmetry of the two sides is common, and in consequence great care must be taken in diagnosis. The introduction of lipiodol into various sinuses may give a clear demonstration of polypi and other lesions in their cavities. During the course of a sinus investigation several other points of information are often available, such as the shape and position of the nasal septum; the size of the turbinate bones and the resulting nasal airway; the presence of unsuspected adenoids may be shown as an encroaching shadow into that of the naso-pharynx. Considerable information regarding the teeth can be obtained such as gross apical infection and the presence of unerupted teeth. The detection of impacted wisdom teeth has sometimes solved an obscure case of neuralgia, headache or some vague group of symptoms.

Chest Diseases. The radiological examination is an essential part of the investigation of chest disease. It is of particular value when history and symptoms suggest the presence of disease and the physical signs are lacking. This is especially true in the case of early pulmonary tuberculosis. The interpretation of the skiagrams, however, requires skill and experience and the practitioner should familiarize himself with the appearances seen in normal cases before attempting to interpret the abnormal.

NORMAL APPEARANCES. If a good film taken in the anterior position is studied, the following structures can be made out:—(1) the soft parts of the chest wall (breasts, pectoral muscles); (2) the bony framework of the chest consisting of the ribs, dorsal spine, and shoulder girdle; (3) diaphragm; (4) the heart and great vessels; (5) the lungs represented by the bronchovascular shadows and the clear spaces between them; and (6) the right horizontal septum.

Soft parts. The shadow thrown by the pectorales major and minor encroaches slightly on the lung fields laterally opposite the second, third, fourth, and fifth ribs.

Diaphragm. The right dome in full inspiration is usually situated at the level of the tenth rib, and the left dome slightly lower. The lung on each side extends downwards below this level, and is therefore partly concealed.

Heart and mediastinum. The trachea is visible above owing to its air content, and normally lies slightly to the left of the mid-line. Below

this the heart and great vessels throw a dense opacity which conceals part of the lung on one side. The right border of this central shadow is formed above by the superior vena cava and below by the right auricle with a distinct notch between the two. At the right cardio-phrenic angle a small triangular shadow is formed by the inferior vena cava. The left border shows a prominence above called the aortic knob or knuckle, and below this there is a lesser prominence caused by the conus of the pulmonary artery. The remainder of this border is formed by the left ventricle. At the left cardio-phrenic angle a triangular shadow is usually seen especially in fat subjects, due to the reflection of the pericardium on to the diaphragm.

Lungs. The lungs on each side, where not obscured by the structures mentioned above, are represented in the film by a fine network of spidery shadows which extends outwards from the lung root or hilum to the periphery. At the lung root these shadows are condensed into an irregular somewhat 'fan-shaped' opacity.

Lung septa. The main or oblique septum is not visible in the anterior view, but the right horizontal septum is projected as a fine transverse line which cuts across the anterior parts of the third and fourth ribs.

CHANGES IN DISEASE. *Pleurisy, pleural effusion, and empyema:* When a simple dry pleurisy with a friction rub is present there may be no changes on X-ray examination beyond restriction of movement of the affected side on screen examination, and sometimes even this is not seen. More often, however, there is some thickening of the pleura, which is evident at the margin of the lung field especially in the costo-phrenic angle. If fluid is present, the shadow becomes accentuated and owing to the negative pressure in the pleural cavity, it extends upwards along the margin of the lung as a lateral opacity, broad below and narrower above. As the fluid accumulates, the shadow increases in size and the heart and mediastinum are displaced to the opposite side unless prevented by the presence of adhesions or fibrosis in the lung.

An exactly similar shadow can be seen in the early stages of empyema, but if the fluid becomes encysted a more circular shadow will be present. A lateral skiagram will be required to localize its position before exploratory puncture. When air is also present in the pleural cavity the negative pressure is reduced and a characteristic fluid level is seen in a skiagram taken with the patient erect. If the accumulation of fluid is large, the whole of the lung field may become opaque, and in such a case the presence of fluid can be diagnosed from the displacement of the heart and mediastinum away from the affected side. In massive fibrosis of the lung with pleural thickening a similar opacity is evident, but the heart and mediastinum are observed to be displaced to the affected side.

Pneumonia. The radiological signs of lobar pneumonia are characteristic and consist of a hazy opacity over the affected lobe which usually appears within the first twenty-four hours and lasts for some weeks from the commencement of the illness. X-ray examination is valuable during the acute stage to show the area of lung involved, and during convalescence in order to determine if normal resolution is occurring. It is almost essential where empyema is suspected. The X-ray appearances in bronchio-pneumonia consist of scattered areas of opacity which appear two or three days after the onset of the illness and which show a tendency to coalesce. In serious cases considerable areas of the lung may become opaque.

Bronchitis and emphysema. The X-ray changes noted are as follows :—(a) Increased clarity of the lung fields especially at the bases ; (b) flattening of the domes of the diaphragm ; (c) increase in the root shadows and basal lung markings from the presence of fibrosis ; and (d) degenerative changes in the bronchi (shown by a lipiodol examination).

Bronchiectasis. Patients suspected of this distressing malady require an X-ray examination which will include not only plain skiagrams of the lungs, but also films obtained after the introduction of lipiodol by the oral or cricothyroid route or by means of a nasal catheter passed into the trachea. In the preliminary films the presence of bronchiectasis may be suspected if a localized 'honeycomb' appearance is present in some part of the lung field. But the true nature and extent of the disease can only be shown after a careful lipiodol examination.

Pulmonary tuberculosis. In this disease the X-ray examination is one of the most important of the various methods of investigation, and it should never be omitted. The radiological appearances vary with the age of the patient and can be described under the headings of :—(a) tuberculosis in children ; and (b) adult type of disease.

Tuberculosis in children. Lesions due to active disease are comparatively rare in children. If the infection involves the mediastinal glands, the root shadows are seen to be enlarged and clouding will be present in the adjacent lung field. The glandular enlargement can be seen in skiagrams taken in the anterior position and also in a skiagram taken in the true lateral position. An interesting group of cases comprises those in which areas of opacity, sometimes corresponding to a whole lobe and resembling pneumonia in appearance, are seen. Skiagrams in other patients will reveal the presence of the adult type of disease.

Adult type of disease. In the stage of early infiltration a small area of clouding about the size of a shilling is visible in the lung field. The commonest site is just below the clavicle but it must be recognised that the disease may also be located in some other part of the lung field and that it may be concealed by the heart shadow unless an oblique view is obtained. These early changes are frequently not discovered by screen examination alone and require skiagrams of the best quality

for their detection. In a difficult case serial skiagrams may be required at intervals of fourteen days to establish the presence of a progressive lesion. In fibro-caseous disease the changes seen in the skiagram correspond closely to the signs of the disease observed clinically and to the pathology. Cavities appear as annular shadows which enclose an area of translucency, and fibrosis is shown by the presence of dense linear opacities.

Lung abscess. •X-ray examination is required in this condition to show the site of disease, which is revealed by the presence of clouding in some part of the lung field, and in order to localize accurately the area of lung involved before bronchoscopic or surgical treatment is undertaken. In the first stages of the disease, the typical appearance is a 'cotton wool' shadow in some part of the lung field. As the disease progresses a cavity may be formed and is then seen as a central translucent area with a fluid level. If resolution does not occur, the X-ray changes become more marked and the whole lung field may be obscured.

New growth. The presence of a bronchial carcinoma is revealed by an opacity, which is due partly to collapse of some part of the lung. Involvement of the mediastinal glands causes an enlarged hilum shadow which can be demonstrated in the anterior and lateral skiagrams. Serial films will reveal a slowly increasing opacity. When the growth starts in the mediastinum an irregular shadow can be seen spreading out into the lung field on each side. If the growth is located in the superior mediastinum close to the great vessels, the appearance at first is closely simulated by an aneurysm. The X-ray appearances of metastases consist either of multiple rounded opacities in the lung field rather like snowballs in appearance or of a coarse generalized mottling which must not be mistaken for the finer mottling of miliary tuberculosis.

Benign tumours form a circumscribed, rounded opacity which is a conspicuous feature in the skiagram.

Abdominal Diseases. From the radiological point of view the easiest diagnosis is gastric ulcer. The characteristic appearance is a niche or projection on the wall of the lesser curvature. The niche may vary in size from a pinhead to a cherry, but in the majority of cases is about the size of a pea. In addition to the niche there are various indirect signs of gastric ulcer, the chief of which are localized pain on pressure, localized spasm and gross disturbance of the rate of emptying of the stomach. In the early days of radiology considerable reliance was placed on the indirect signs because in many cases the niche could not be brought into view when situated deep on the posterior wall of the stomach. A modern method of examination of the gastric mucosa, generally known as 'dosed compression' has eliminated this difficulty. The technique of 'dosed compression' consists in introducing a small quantity of a watery solution of barium into the stomach, and under the screen slowly squeezing this mixture

over the gastric walls so as to outline the gastric rugae. In cases of ulcer, the rugae of the lesser curvature instead of taking their normal linear course converge to a point above the ulcer and diverge from a point below the ulcer. In addition to this finding the rugae of the greater curvature are generally seen to be raised and thickened, an appearance aptly described by Berg as an ulcer gastritis. Examination of the gastric mucosa alone gives no evidence of the tone, peristalsis or rate of emptying of the stomach and should therefore only supplement the ordinary barium meal examination in selected cases. The size of the niche is not an adequate guide to the true size of the ulcer and is not a reliable guide to prognosis. It was formerly thought that a large niche was in favour of the ulcer being malignant and irrespective of this factor, that a large niche was an indication for surgical rather than medical treatment. A careful screen examination of the gastric mucosa will generally show whether a niche is malignant or not, and every radiologist has seen craters as large as a florin disappear under adequate medical treatment.

The diagnosis of early carcinoma of the stomach is perhaps the most difficult problem for the radiologist. The earliest sign of a small area of malignant infiltration must be an interruption of peristalsis over the affected area. Advanced gastric carcinoma produces on a radiograph a characteristic appearance known as a filling defect; in other words there is a large area of the stomach which is not covered by barium. There are innumerable types of filling defects depending on whether the neoplasm is of the fungoid or scirrhous type. As a rule malignant filling defects have a ragged outline and there is complete absence of peristalsis over them. Malignant filling defects can be simulated by spasm, by adhesions and by rare lesions, such as adult pyloric hypertrophy and gastric syphilis. Syphilis of the stomach is seldom diagnosed by X-ray alone.

DUODENAL DISEASE. Duodenal ulcers are usually situated on the posterior wall and therefore cannot be shown in profile like gastric craters. They are most readily visible when there is associated spasm, and fortunately this is usually the case. The characteristic appearance is an indentation on the greater curvature of the cap, retraction of the lesser curvature and between the two a small dense fleck of barium. The fleck is tender on pressure and may be visible for some hours after the stomach and duodenum have completely emptied. This fleck is the only diagnostic sign of duodenal ulcer and every effort should be made to get an X-ray picture of it. If there is strong indirect evidence of ulcer, such as deformity of the cap and pain on pressure with reflex irritation of the stomach, the duodenum should be examined further by means of serial skiagraphs.

JEJUNAL ULCER. The X-ray diagnosis of jejunal ulcer as a sequel to gastro-jejunostomy has been considerably improved by the compression

technique and the demonstration of the mucosa at the site of the anastomosis. As in the normal stomach and duodenum, the diagnostic appearance is a persistent fleck with thickened rugae converging on it. When a jejunal ulcer is visualized by X-rays the meal should be carefully followed and if necessary an enema should be given shortly after the meal to determine whether such adhesions are present or not.

APPENDIX. X-ray examination of the appendix is reliable in 95 per cent. of cases. In about 80 per cent. of cases the appendix fills readily during an ordinary barium meal examination; of the remaining 20 per cent. 15 can be filled by following the barium meal with a saline aperient or by giving a barium enema, and the remaining 5 per cent. cannot be filled by any method. Failure to fill suggests, but is not diagnostic, of a morbid change. The radiological signs of an inflamed appendix are 'rosary bead' appearance due to faecoliths, kinks which cannot be straightened out, fixity of the tip of the appendix and pain on pressure.

LARGE INTESTINE. For the investigation of diseases of the large intestine both a barium meal and a barium enema are desirable. Mucous colic is perhaps too frequently diagnosed from X-ray appearances. Characteristic findings are stated to be:—(1) Rapid filling of the colon on barium meal examination, *i.e.*, the meal reaches the iliac colon in 6 to 9 hours instead of the normal 16 to 24 hours; (2) Spasm of the distal half of the colon giving a ribbon appearance; (3) Complete evacuation of the meal in 24 hours or less; (4) A narrow lumen of the pelvic and descending colon with absence of haustration on enema examination; (5) Pain on pressure over the descending colon. Unfortunately all of these signs can be produced by the injudicious use of aperients and enemas, a prevalent addiction which renders the accurate X-ray diagnosis of mucous colitis very difficult.

Ulcerative colitis has such a typical picture that X-ray examination is only used to determine the extent of bowel involved and the progress of the disease under treatment. A barium enema, but not always a barium meal, gives characteristic appearances. The enema appearances are:—(1) Absence of haustration; (2) dilatation of the lumen with intermittent contractions giving a 'string of sausages' appearance; (3) non-homogeneous filling of the gut, the barium lying in flecks on the oedematous mucosa; (4) large flat flecks which are actual ulcer craters. The mucosa of the large intestine and the actual craters can be visualized by using the following technique. The patient is given a thin barium enema and makes an evacuation shortly after the injection. This evacuation expels one third to one half of the barium. Air is then gently pumped in with a Higginson's syringe and the residual liquid barium is evenly distributed over the intestinal mucosa. The introduction of the air is not a comfortable procedure and is seldom necessary in a case of ulcerative colitis. The method, however, is of great value for the detection of single ulcers (possibly malignant) and bleeding polyps of the lower bowel.

Diverticulosis and diverticulitis can give rise to the same clinical findings as carcinoma of the large intestine, and X-ray examination is the most useful method of making the differential diagnosis. The barium enema is more valuable than the barium meal. There are two diagnostic appearances:—(1) A saw-tooth edge of the affected area of the intestine. (2) The demonstration of the diverticula. Both are usually seen together, but sometimes the saw-tooth edge is seen alone.

Carcinoma of the large intestine. Generally speaking the X-ray appearances go hand in hand with the symptoms—the more severe the symptoms the more obvious are the X-ray appearances—but occasionally the radiologist discovers an entirely unsuspected intestinal neoplasm. The earliest signs of carcinoma of the large intestine are spasm or interference with peristalsis in the affected area. The characteristic sign of carcinoma is a filling defect which may or may not be associated with distension of the bowel proximal to the defect. The filling defect, like that seen in carcinoma of the stomach, is usually irregular in outline and may vary in extent from half an inch to a foot.

GALL BLADDER. The frequency of gall-bladder disease and the influence it exerts on other abdominal organs has been revealed by the introduction of cholecystography. This has been described in detail elsewhere. (*Practitioner*, July, 1935).

GROSS APPEARANCE OF INFECTED WOUNDS

It commonly happens that the physician or surgeon must decide by the gross appearance of a wound or ulcer what the infecting organism may most likely be.

STAPHYLOCOCCUS INFECTION. During the early stage of the typical staphylococcal infection the tissues are hard and indurated. Later this area will either go back to the normal condition or it will soften in the centre and a slough will form. This slough is composed of dissolved tissue, pus cells, and bacteria, and is surrounded by a zone of tissue and vascular response which is called 'pyogenic membrane.' The pus is usually thick in consistency and creamy yellow in colour, being the most common form of pus that is seen. Occasionally the pus may have a pale greenish colour or may show streaks of blood.

STREPTOCOCCUS INFECTION. Wound infections due to various strains of *Streptococcus pyogenes* are the constant dread of the surgeon. Staphylococcal pus was often described as being 'laudable pus,' while that now known to be due to the streptococcus was called 'pernicious pus.' This pus is thinner, may be lumpy or curdy; often streaked with blood, black, red, brown, or dirty colored.

ESCHERICHIA COLI INFECTION. These lesions are usually seen only in those who have been long in bed, are considerably debilitated, and of low resistance. The lesions are more commonly near the pelvic organs.

The tissues about the lesion are usually not very badly inflamed, the pus is greyish and rather slimy, and has an odour commonly described as 'fæcal' though this is not strictly correct. Nearly always *Staphylococcus albus*, and often *Staphylococcus aureus* are associated. The granulation tissue is indolent, grey and usually oedematous. The lesions are not often highly destructive, but may persist for a long time.

PSEUDOMONAS AERUGINOSA (BACILLUS PYOCYANEUS) INFECTION. These infections present a very striking appearance and are likely to be quite alarming to the patient and his family. The pus produced is of a bluish-green appearance and stains the dressings. Unless the patient is reassured he is likely to think that gangrene has taken place and that his case is hopeless. As a matter of fact the infection is rarely of any consequence and the patient may be reassured.

CLOSTRIDIUM TETANI INFECTION. It is a matter of common knowledge that a mere scratch may suffice to cause 'lockjaw'. More commonly, however, a wound that causes tetanus shows evidence of having had pus and a crust over it, or a foreign body in it. The diagnosis of tetanus is made, however, not from the wound but from the systemic symptoms, the history of a scratch or an injury being merely confirmatory. A piece of tissue removed at biopsy may be useful in making a diagnosis. When crushed or sectioned typical bacilli may be seen when a bacterial stain is used.

ANTHRAX INFECTION. (Malignant pustule). This dangerous infection resembles a boil at first but soon changes in appearance to a dark or black necrotic lesion with serosanguineous or seropurulent contents and is surrounded by an 'angry' red area. If it is promptly excised the patient will usually recover but if neglected the outcome is fatal as a rule.

CLOSTRIDIUM WELCHII INFECTION: (Gas gangrene). The part is commonly much swollen, and greatly discoloured. A 'bronzing' of the skin is characteristic. Crepitation of the tissues due to the presence of tiny bubbles of gas makes the diagnosis nearly certain. The exudate from the wound is commonly a brown fluid that contains many gas bubbles. A fætid putrefactive, or acid odour is common.

CLOSTRIDIUM HISTOLYTICUM INFECTION. This is a rare condition which produces very marked proteolysis of the tissues affected, without producing general symptoms of any consequence.

CORYNEBACTERIUM DIPHTHERIÆ WOUND INFECTION. This is a very serious condition, but fortunately is rare. When there are symptoms of marked intoxication as in diphtheria and the patient has a wound, close examination of the latter is indicated. Smears should be made, and there should be no delay in giving antitoxin if there is anything that resembles a diphtheritic membrane in the wound.

PASTURELLA TULARFENSIS INFECTION. A papule first appears, then an ulcer and an ugly black slough. Regional lymph glands swell, and systemic symptoms appear

HEMOPHILUS DUCREYI INFECTION. The soft chancre consists at first of a red papule which in two or three days becomes a vesicle surrounded by a zone of 'angry' hyperemia. In four or five days the lesion becomes a pustule and then the cuticle breaks through, forming an ulcer. This ulcer is rather characteristic in that it has a ragged, inflamed, and undermined margin, but shows little induration. It heals in about three weeks if everything goes well and it is given the proper care.

NEISSERIA GONORRHOEA INFECTION. Thick yellow pus, with underlying tissue very red.

BED-SORES. It is commonly said that these are simply pressure sores caused by the continuous local anæmia in the patient with a poor circulation and not enough fat to pad the skin and bones. The bacteriology of bed-sores has usually not been taken into consideration. Examination of a rather large number of these sores in recent years has revealed that all of these lesions contain at least the *Staphylococcus aureus* and *Escherichia coli*. *Staphylococcus albus*, *Pseudomonas aeruginosa* and a great many other contaminating and saprophytic bacteria are also commonly found, but the significant ones are undoubtedly *Staphylococcus aureus* and *Esch. coli*. These organisms doubtless account for the destructiveness of the lesions, for the purulent discharge and for the pungent faecal odour—a particularly disgusting and offensive odour. These lesions are probably caused, as is commonly stated, by the local anæmia and local trophic nerve disturbances, or irritation, but it is the action of bacteria that causes them to have the characteristics that are so commonly seen.

If the bacterial infection can be corrected these lesions will heal fairly promptly, provided, of course, that the condition that caused the sores has been removed. Bacteriophage active against cultures of *Staphylococcus aureus* and *Esch. coli* has been successful to a striking degree in cleaning these dirty, ugly sores, checking the offensive discharge and odour and in bringing about the development of healthy granulation tissue, and healing with the minimum of scar. Bacterial infection is not the sole cause of these sores, but it is always present after the sore has developed, and if corrected will greatly foster the healing process. Patients with diabetes, syphilis, arteriosclerosis, trophic nerve disturbances, and senile changes of marked grade have shown complete healing, usually in spite of the fact that their primary condition was unimproved or definitely worse. The treatment of decubitus ulcers is bacteriological as well as physical.

Site of focal infection. (1) The faucial tonsils, the peri-tonsillar tissues and supratonsillar fossae. In this may also be included the lymphoid tissue embraced in the pharyngeal tonsil and elsewhere in the nasopharyngeal space. The abundance of this tissue in the child probably explains the frequency of infections like acute rheumatic fever, diphtheria, tonsillitis, etc., in the earlier periods of life. The fact that chronic septic focal infection may lie latent in the tonsillar

tissue has not been generally recognised. That this focal infection may produce a chronic systemic disease is established by clinical experimentation. (2) Abscess of the gums and alveolar sockets, pyorrhoea alveolaris and septic types of gingivitis may also cause systemic disease of various types. (3) The various sinuses about the head—maxillary, ethmoidal, sphenoidal, and frontal—may also harbour focal infection and cause systemic disease. (4) Bronchiectatic and pulmonic cavities due to chronic disease may also produce chronic systemic infections. (5) Chronic ulcers of the gastro-intestinal tract, specially of the bowels. This source is probably rare and more problematic than that of any other systemic infection. (6) Chronic appendicitis. Chronic catarrhal appendicitis may produce not only the local discomforts including disturbance of the functions of the digestive organs, but may also be a focal source of systemic infection with the damage done chiefly to the cardiovascular apparatus. (7) Cholecystitis and cholangitis, with or without calculi, have been recognised as sources of systemic infection, the brunt of the damage apparently falling on the cardiovascular apparatus and kidney. (8) The urinary tract, including the pelvis of the kidney, the bladder, and more particularly the prostate gland. Pyelitis of whatever type, even when there is only moderate obstruction of the drainage of the kidney pelvis, may produce myositis, arthritis, neuritis, etc. (9) Genital tract. The prostate and seminal vesicles are a common source of infection of gonorrhoeal arthritis and probably of ordinary septic infections. The fallopian tubes and the uterus are less commonly a source of chronic systemic disease in all probability. It is said that the parametrium is a more common focal source of infection. (10) Local, septic, submucous and subcutaneous foci anywhere in the body may be a source of systemic disease.

Systemic results of focal infection. (1) Chronic arthritis is one of the most common results; (2) nephritis, both acute and chronic; (3) cardiovascular degenerations; (4) chronic neuritis and myalgia (myositis).

INTEGRATION OF THE ENDOCRINE SYSTEM

To state briefly the view of the integration of the endocrine system there is doubtless an autonomous activity of these glands according to the steady biochemical demand of the body, but their activity can be profoundly modified and extensively controlled by centres in the diencephalon which are largely concerned with emotional expression. These centres may operate directly through the sympathetic nervous system (indeed, the hypothalamus has been called the head ganglion of the sympathetic) or indirectly through the chemical activities of the anterior pituitary. The anterior pituitary forms two basic secretions probably of a protein character, one being stimulating the other inhibitory in effect. They correspond in fact to

Sharpey Schafer's original distinction between a hormone and a chalone. It is suggested that the former is produced by the eosinophile, the latter by the basophile cells. These basic secretions are capable of chemical modification according to the needs of the body, and are then ready to stimulate or restrain the secretion of simpler hormones by the other endocrine glands, including the post-pituitary. It may be as Zondek maintains, that the hormones circulate in an inactive form, only becoming activated when they reach their destination. This indeed might explain some of the observations on the alleged hormone-antihormone linkage. Certain it is that their destination is decided by some peculiar receptive capacity in the structure on which they act, catalytically or otherwise. What determines that receptive capacity, we do not know as yet. But we can say that the whole process appears to be a special case of the general law that nervous stimuli, whether passing from the diencephalon to the pituitary, or down neurons to pre and post-ganglionic endings, act through the intermediary of chemical substances locally produced. And there may be some further support for this view in the fact that, in one instance, the same substance, adrenalin, is the final product of either hormonal or nervous activity. (*Lancet*, 1935, p. 1160).

Endocrinology in Relationship to Interpretation and Understanding of Common Symptoms. Advances in the study of glands of internal secretion cannot be judged solely or chiefly by the extent to which they lead to successful organotherapy but more by the profound influence they have on the understanding and interpretation of common symptoms. Consideration of their relation to hypertension, obesity and disturbances in carbohydrate metabolism is of especial importance because of the frequency of such manifestations, because they are often encountered in the same individual and because in certain striking instances they are directly attributable to pathological changes in the hypophysis or the adrenals. Although participation of these and other glands of internal secretion must be suspected in many cases of high blood pressure, obesity and diabetes, caution is necessary lest the newer knowledge be applied prematurely and too extensively in surgical and radiological treatment. (*Jour. Amer. Med. Assoc.*, 1935, Vol. 105).

PYROGENIC (FEVER PRODUCING) SUBSTANCES IN DISTILLED WATER (p. 42)

The fact that certain bacteria can grow in distilled water is well known. The work of Seibert, and of Broun and Seibert (*Am. J. Physiology*, 71, pp. 621-629) has done much to explain the fact that intravenous solutions made from stale contaminated distilled water can cause dangerous reactions and may even cause serious injury even though it is sterile at the time the injection is made. It was found that about 50 per cent. of distilled waters from different laboratories produce fever

when injected intravenously into rabbits. The fever-producing substance is a bacterial product and can be removed by distillation.

The bacteria at fault can be divided into three groups (25 strains studies) :—

I. All strains studies which were not responsible for fever production are put into this group, which is in turn divided into two groups. (A) Red chromogenic bacilli, and (B) Chromogenic micrococci.

II. The strains which were responsible for mild fever seem to be related to Jordan's group XI, and are characterised by the fact that they are bacilli which do not liquefy gelatin, and do produce alkalinity in milk.

III. Strains responsible for severe fever and even death all seem to fall within the group X described by Jordan. They are somewhat similar to the coli group except that no gas is produced on sugar broth and no indol is formed. They produce acid in milk, but do not liquefy gelatine. They seem to belong to an unnamed tribe of Bacteriaceae belonging somewhere between *Erwineae* and *Bastercae*.

As to the chemical nature of the pyrogen, it is destroyed very slowly by heat alone, but readily by heat in the presence of acid or alkali. It can be concentrated under diminished pressure, and temperature under the boiling point, the amount of concentration being tested by the degree of rise in temperature in rabbits when it is injected.

Anaphylactic reactions were produced in rabbits sensitized by concentrated pyrogenic water, while non-sensitized rabbits did not respond similarly. Similar shock reactions were produced in rabbits by the first injection of aqueous Berkefeld filtrates of the two strains of bacteria isolated from pyrogenic waters.

This work does much to explain the very annoying chills which so often follow intravenous medication. Only distilled water which has been sterilised immediately after distillation and then stored in a germ proof container is safe for intravenous use. Such water may be prepared in any well-equipped laboratory or surgery or may be bought in ampoules. All connections should be thoroughly cleaned before being sterilized. Rubber tubing should be thoroughly brushed on the inside with a slender tube brush. It should then be rinsed thoroughly and boiled with the apparatus. There are doubtless other causes of 'chills' after intravenous medication, but certainly the most common one is the presence of a pyrogenic substance in the distilled water, a result of bacterial growth.

In making solutions for intravenous use, use only water that was sterilized and sealed immediately after having been distilled.

CLIMATE AS A DISEASE FACTOR

According to the meteorologists the temperature, moisture and movement of the air, the amount and quality of the light, the rainfall and barometric pressure form the chief items of a group of conditions

which, taken together, constitute the weather of a place at any given moment; the average weather of a place throughout the year constitutes its climate. It is, however, advantageous to use the word "climate" in the loose, popular way as indicating the general weather conditions of the locality at a given season rather than to attempt to summarise the average weather for the whole year.

CLIMATE AND HEALTH. Climatic conditions affect the health of human beings in several ways:—(a) *Directly.* The conditions of air temperature, moisture and movement taken together may be favourable to the vitality and energy of the body, they may act unfavourably by lowering resistance to disease, or they may actually cause diseases like heat-stroke or frost-bite. Light may act in a favourable or unfavourable manner; excess of light gives rise to solar dermatitis and night blindness; defect of light is one of the causes of rickets and osteomalacia. Light may increase vitality when it falls on the body in suitable amounts, whereas deficient exposure to light may be a cause of lowered vitality. (b) *Indirectly.* The crops of a place, and hence the food supply of the people, depend largely on climate. Insect life is much influenced by climate. Diseases which are conveyed by insects can only be transmitted when the climatic conditions are suitable for the existence of the insects, for the development of the disease parasites in their bodies, and for their ability to bite human beings. Bacteria which have to pass through the air on their way from person to person are also affected by the temperature, moisture, and movement of the air, so that climatic conditions may greatly influence the spread of 'droplet' infections, and even in some cases the spread of contact infections. Much attention has been devoted to the influence of climate in connection with the prevalence of diseases like malaria, plague, relapsing fever, small-pox, cholera, etc. There is doubt regarding the association between climate and cholera transmission, though the influence of air temperature and moisture on the spread of this disease is not understood. Rainfall for instance may favour transmission or cause its disappearance.

GENERAL EFFECTS OF TROPICAL CLIMATES ON THE HUMAN BODY. There is a most unfortunate impression that any sensation of cold ought to be avoided: the origin of this mistaken belief is that many fevers start with a feeling of chilliness, and so it is natural for people to think that chill has been the actual cause of these fevers whereas it has merely been a symptom of the onset. The dread of the slightest sensation of cold on the surface of the body is responsible for a vast amount of ill-health; it leads to the closing up of doors and windows, and so conduces to the spread of droplet infection; it also causes people to coddle themselves so that they lose the power of reacting to a fall in air temperature and therefore become liable to suffer ill effects from slight exposure to cold. The body ought to be capable of resisting changes of temperature; it cannot attain to full vigour unless

exposed to these changes within reasonable limits. In very hot weather, especially when the high air temperature is accompanied by excessive air moisture and lack of movement of the air, the body has to contend against a set of unfavourable conditions: the cooling effect of the air, combined with evaporation from the body surface, may be just sufficient to keep the temperature within normal limits, even when the muscles are relaxed and all the other tissues are inactive. In such conditions exercise is almost impossible, as bodily work is always accompanied by a great increase in heat production, the appetite is feeble, because assimilation of food causes increased heat production; the body has no opportunity of reacting to cold and hence loses the power of doing so. Persons exposed for long periods to these conditions tend to become enfeebled and lose their resistance to disease. Their mental energy is also sapped: they often become fatalistic and cease to make any effort to improve their climatic environment. In cold countries steps are taken to heat dwelling-houses, but in the tropics artificial cooling of houses is regarded by many as a preposterous suggestion, although it is much more necessary for the maintenance of health than artificial heating in cold climates.

SUNLIGHT AS A FACTOR IN CAUSING HEALTH AND DISEASE. The rays of the sun have very different properties according to their wave-length. These are shown in the following table.

Properties of the Sun's Rays

	Visibility.	Chief actions.	Diseases caused.
Heat rays.			
1. Infra-red.	Invisible.	} Heating.	{ Heat exhaustion.
2. Red.	Visible.		
Luminous rays.			
3. Orange	Visible.	Chiefly illuminating	{ Glare headache.
4. Yellow.			
5. Green.			
Chemical rays.			
6. Blue.	{ Visible.	{ Stimulating and anti-rachitic in moderate doses.	Solar dermatitis.
7. Indigo.			
8. Violet.			
9. Ultra-violet.	Invisible.	Irritant and destructive of tissues in excessive doses.	Pigmentation.

* **TROPICAL SUN.** In the tropics all the rays of the sun tend to be more powerful than in cool climates, but they have no mysterious dangerous properties, such as are often attributed to them. The prevailing idea that certain rays of the tropical sun can penetrate through

considerable thicknesses of cloth or other material is a myth. Any fabric which cuts out the visible rays will also cut out the ultra-violet rays. The strongest tropical sunlight, after passing through a thin white muslin cloth, acts less powerfully on the skin than the unscreened rays of the noon-day sun in England. The real harm done by the rays of the tropical sun consists in their powerful heating effect on the body, so that when a person is exposed to trying atmospheric conditions the direct heating action of the sun's rays adds greatly to his discomfort and also to the risk of heat-stroke. The wearing of a broad-brimmed pith helmet in bright sunlight is a highly rational procedure—it protects against heat and glare; but to wear a 'topi' in a well shaded verandah, or when the sun is near the horizon, is absurd. In the cool of the morning a reasonable exposure of the body to light is very useful, though excessive exposure to the ultra-violet and heat rays throughout the day is most injurious.

CLOTHING IN THE TROPICS. It would be much easier to devise suitable clothing in the tropics both for men and women if the decrees of fashion could be ignored. In existing conditions all that can be done is to rectify the more glaring defects. There are places in the tropics in which the most suitable 'clothing' would consist of a large umbrella; but idyllic simplicity of this kind is impracticable, so we have to fall back on the next best thing, which consists of white, loose clothing of light texture. A loose tennis shirt of thin white cotton kept open at the neck, a loose pair of white cotton 'shorts' supported by buttons fixed on the shirt, and a large well-ventilated pith helmet are most suitable for wear in the day time. Long trousers are necessary after sundown to protect the legs against mosquito bites. It is even more difficult to devise suitable clothing for ladies than for men, but with the passing of the dangerous short skirts, which left the legs exposed to mosquitoes, the day clothes of European women in the tropics are now more suitable on the whole than those ordinarily worn by men. When a coat is worn braces are more suitable than a belt; the clothing should not constrict any part of the body, especially the neck and waist. Special materials like 'Solaro' have no great advantage over ordinary fabrics; white has the valuable property of filtering out the heat-rays better than any other colour, and the ultra-violet rays which are allowed to pass through any ordinary cloth are so reduced in intensity that they are incapable of doing any harm. Pale blue comes next to white in its power to cut out heat-rays, then comes khaki, while black is least effective of all.

In malarious places a really important point is that the body should be protected as completely as possible against mosquito bites after sundown. Chill has to be guarded against when there are sudden changes in temperature: the abdomen is the part most liable to damage by chill. A light woollen shawl or blanket should be wrapped round the abdomen at night, even when the weather is so hot

that no other bed clothing is endurable. There is often a sudden fall in the temperature at night in the tropics; if the abdomen has not been protected a sharp attack of diarrhoea or a lighting up of an old dysentery may result. After exercise it is usual for people to put on heavy sweaters and flannel coats. This practice may be necessary for those who have not trained their bodies to react to changes of temperature, but for the healthy person who has not coddled himself a tepid bath and a change into light clothing is the best procedure. A Turkish bath and perspiration produced by heavy woollen clothes is both nasty and unhealthy. The sensation of coolness should be sought after rather than dreaded, provided that the abdomen and chest are protected and local chilling of one part of the body is avoided. The general rule for the tropics is "keep as cool as you can, as long as you can"; if you have kept cool and accustomed yourself to react to changes of temperature, there is little reason to dread the chills which are such bugbears all the world over. It is not suggested that chills should be ignored. Those who have kept themselves in hot house conditions for years may suffer from very serious illness if they are exposed to cold; they must expect to pay the penalty for having adopted wrong habits; the acquisition of these is the initial mistake. The importance of local chilling of the body in lighting up fibrositis, respiratory infections, etc., is well recognised, but war experience has shown that exposure to cold and wet can be endured by healthy persons with surprisingly little ill effects. The fashions in women's dress which involve exposure of the neck and chest to cold have not resulted in the expected crop of pneumonia and sore-throat.

HEAD WEAR. A good *topi* protects the head and a great part of the body from the heat-rays of the sun, and so helps to ward off heat-stroke. The local heating of the head and surface of the brain by the noon-day tropical sun may be very harmful in itself, apart altogether from the extra heating effect which is produced on the body as a whole. Corrie in Senegal has made some interesting observations on the air temperature inside various kinds of head-gear in noon-day tropical conditions. The records were:—(1) Pith helmet, with white cover and ventilation 35.6°C. (2) Straw hat, with white cloth cover (French Marine pattern) 37.5°C. (3) French non-commissioned officer's kepi, without cover, but with ventilating holes 39.0°C. (4) French sailor's cap, with white cover, 40.0°C. (5) French sailor's cap, without cover, 41.0°C.

A large thick pith *topi* with effective ventilation round the rim and in the top is the best form of head-gear. An umbrella is even better than a *topi*, as it protects a much larger area of the body from the heat rays of the sun.

HOUSING IN THE TROPICS. Where the prevailing climate is one of intense dry heat, insulated roofs and walls, lofty rooms provided with doors and windows which can be properly closed in the heat of the day are essential. Single-storied bungalows with low plinths are better

than two-storied houses as the earth under the house serves as a reservoir of 'coolness' for a considerable time after the onset of the hot weather. The house should be closed early in the morning and opened only when the outside temperature falls below that of the inside. Clerestory windows, high up in the walls, are useful in allowing the heated air to escape during the night; like the other windows, they must be closed during the heat of the day. Where the prevailing heat is moist and excessively high air temperatures do not occur, the insulation of the roof and walls is of less importance; the essential point is to construct the house so that plentiful through ventilation can be secured during the whole day and night. Air which is heated by contact with the roof or walls is so rapidly swept away by the through draught of air that it has no influence on the air temperature of the lower part of the room. No single type of house can be prescribed as suitable for all tropical countries; each place has its own special conditions which must be studied. In malarious places the houses must, of course, be mosquito-proof in an intelligent manner.

ARTIFICIAL COOLING OF HOUSES. In large industrial centres artificial systems of cooling are gradually being introduced into offices, hospitals, operating theatres, places of amusement, etc. The first plant of this kind in India was installed in the Calcutta School of Tropical Medicine. It has been in regular use since the opening of the school in 1920, and has proved very successful. The incoming air is cooled by being blown by a fan over the cold pipes of a refrigerating plant. In the cooling chamber the temperature of the air is lowered to such an extent that much moisture is precipitated. The air is then forced into the room where its temperature rises several degrees so that it becomes relatively dry. Air is constantly being drawn from the room by the same fan which forces the cool air into the room; some of this air is returned to the room after being cooled again, but provision is made for the introduction of an ample supply of fresh air through a gauze filter contained in the circuit. The net result is a regular supply of cool, fresh, dry air, free from dust and insects. No fans are needed, and books, delicate instruments, etc., keep in as good condition as in temperate climates. The cost of installation to cool a whole house would be prohibitive, but one or two rooms could be cooled by an inexpensive plant on the same lines. In the case of offices, hospitals, barracks, etc., a system of central cooling will probably be found practicable in the near future. Already several commercial concerns are specialising in 'air-conditioning' plants, but these are still too costly for general use. In places where dry heat prevails, a simple system based on the principle of the 'thermantidote' will suffice. A good electric exhaust fan like the 'Sirocco' is fitted into a hole in a door. To the outside of the door is fitted a frame slightly smaller than the door and about eighteen inches in depth. To the frame a *khush-khush* screen is attached in such a way that all the air

sucked into the room by the fan must pass over the screen, which is kept constantly moist by a drip from a cistern placed overhead in a shaded place. This system will not be effective when the outside air is damp, but in this case the heat will be less intense and ordinary fans will suffice. In many cases the flow of air created by the two fans of the installation will be enough if the flow of water over the *khus-khus* screen is cut off. In places which have a cold winter and hot summer both conditions can be provided for simply by using a coil of hot-water pipes instead of the *khus-khus* screen in cold weather. The cooling effect of evaporation of water has not been adequately exploited in dry, hot places. It is deserving of further study and experiment.

The Cooling of Railway Carriages. The air of railway carriages is often dangerously hot, especially in places where intense dry heat prevails. Blocks of ice do little to mitigate discomfort, as the air which is cooled by them falls to the floor and is rapidly swept away through the chinks under the doors. Rather better results can be obtained by keeping the carriage floor constantly wet. To cool a railway carriage exactly the same principle as has been suggested for cooling a room may be adopted. Carriages of the Pullman or refreshment car type are most suitable; in the front of the carriage can be fitted a *khus-khus* screen, kept moistened by a drip of water from a cistern. The movement of the train will provide ample air-flow through the screen if a small air-shoot is fitted.

Very effective cooling can be obtained by spreading a wet towel over the naked body and turning a fan in the direction of the bed on which the person is lying. After a few minutes the air under the towel becomes positively cold and there is risk of local chill if the towel comes in contact with the chest or abdomen. To obviate this a surgical cradle can be placed over the body and a large wet towel spread over this so as to shut in the cooled air on all sides. For invalids an arrangement of this kind may be absolutely necessary in extreme heat. (*Tropical Medicine*—Rogers & Megaw, 1935).

DIET IN THE TROPICS (p. 146)

Alcohol in the Tropics. Alcoholic excess is responsible for more disability and shortening of life among Europeans in the tropics than any of the great tropical diseases. In strictly limited quantities alcohol does no harm, it may even be useful in certain circumstances, yet the great majority of people who admit alcohol to their dietary in the tropics suffers to some extent sooner or later. The mischief done by alcoholic excess is well known and need not be emphasised; the evil that is wrought by 'moderate drinking' is far more important as it is not generally recognised. The real danger of alcohol consists in its tendency to give rise to habit formation, and unfortunately nobody knows

till he tries whether or not he is one of the people who will acquire the habit. Alcohol is usually taken, to begin with, because it is customary to do so and nobody likes to be considered a crank who refuses to adapt himself to the social customs of his fellow-men. Then the treating system which is almost universal induces most people to drink more than they really care for, and so they are compelled to experience the dangerous effects of the drug. They find themselves pleasantly exhilarated and soon they have to resort to alcohol to prevent the after depression which results from the use of the insidious drug. Worst of all, those who are 'under the weather' for any reason or who suffer from an inferiority complex find release from their disabilities in a large dose of whisky or brandy. They are really happy and contented only when under the influence of alcohol. Gradually increasing doses are needed to produce the desired feeling of well-being, and in extreme cases the result is a condition of chronic alcoholism. Even people who would be indignant if it were suggested that they drink to excess suffer very definite injury from their 'few pegs a day.' Every medical man should do his utmost to abolish the treating custom in the interests of the men for whose health he is responsible. He should also warn every young man of the dangers of alcohol, and best of all, should set an example by avoiding those dangers himself. It has been abundantly proved that alcohol is not necessary in the tropics, although there is no evidence that a small peg twice daily has any harmful effect in itself. The cocktail habit is specially pernicious: concentrated alcohol taken on an empty stomach is far more harmful to the stomach and liver than well-diluted whisky pegs. Some diseases are definitely associated with alcohol, such as alcoholic neuritis, delirium tremens and cirrhosis of the liver. In the cases of amoebic hepatitis, liver abscess, pneumonia, heat stroke and tropical neurasthenia, alcohol is of importance as a predisposing factor. Alcoholics take anaesthetics badly and run exceptional risks from surgical operations. Indigenous races of tropical countries should be discouraged from the use of alcohol in any circumstances; they are notoriously liable to become addicts to the drug.

Dietetic Errors of Indigenous Races. The chief defects consist in the excessive bulkiness and low nutritive value of the diets. People who live chiefly on rice often take 30 to 40 oz. daily; this, when cooked, forms a very bulky diet which causes distention of the stomach and is incompletely digested. McCay, who carried out important investigations into Indian diets, made the following observations:—(1) The absorption of proteins from cooked rice is actually diminished when excessive quantities are eaten, for example, 8½ gm. were absorbed when 19 oz. of rice were eaten daily, but only 6½ gm. when 30 oz. were consumed. The larger ration does not make up for the poor quality of proteins of the diet but rather the reverse, while the excess of carbohydrates upsets the balance of the

diet. (2) Certain vegetable sources of protein are unsatisfactory; from a diet of millets, dāl and vegetables containing 16 gm. of protein in all, only 9½ gm. were absorbed, whereas from a diet of wheat containing 16 gm. of protein as much as 13 gm. were absorbed. (3) Unsuitable methods of cooking and disorders of the alimentary system caused a reduction in the absorption of proteins. (4) Great variations in physique and fitness were found among the races using different diets. Europeans and Sikhs who absorbed over 0.25 gm. of protein per kg. of body-weight were far more robust than Bengalis who absorbed only 0.11 gm. per kg. The average Sikh diet approaches closely to good European standards: it consists of milk ¼ pint, wheat 24 oz., butter or ghee 2 oz., dāl 3 oz., vegetables 6 oz., and meat 4 oz. An unexpected finding was that the low protein absorption of the Bengalis was associated with increased prevalence of degenerative diseases of the kidneys. The reason for this is probably malnutrition of the kidney cells.

The nutritional defects of indigenous populations are easy to discover but difficult to rectify; they are closely associated with poor economic standards of life, which in turn are connected with social customs, especially early marriage and unrestricted procreation of children. So long as immature boys and girls marry and proceed to have large families before they are able to maintain them, there is no prospect of economic improvement; any increase in the production of food will quickly be neutralised by a corresponding increase in the population. The solution of the problem lies in a rational education directed towards showing the rising generation how to adapt themselves to their environment by later and more provident marriages or by limiting the number of children in some other way. The chief dietetic error which prevails among the richer members of the tropical communities consists in excessive consumption of carbohydrates, especially in the form of easily absorbable sugars. This fault, when combined with lack of exercise, leads to obesity and finally to diabetes.

Drug Addition. See page 1116.

Invalid Diet in the Tropics. A good supply of fresh milk must be provided in every hospital. Another important practical point is that invalid diets are often deficient in the anti-scorbutic vitamins; a standing order should be observed in all hospitals that every patient who is on an invalid diet must be given the juice of an orange daily or a corresponding dose of vitamin C in some other form. The prejudices of patients may give rise to a certain amount of difficulty. Many of them regard rice as the only suitable staple article of diet, so that a good deal of persuasion may be needed to induce them to take other food.* Many Indians regard milk as unsuitable for those who have a cough, because of a traditional belief that the milk becomes converted into phlegm. Many patients also object to milk because they find that it causes diarrhoea. The explanation of this prejudice is that milk is

usually regarded as a drink and is taken in addition to a full diet, with the result that the suitable quantities, either alone or as a substitute for other food, it does not cause diarrhoea in the tropics, any more than in cold countries. Milk in the tropics is often boiled for a long time; care must be taken to ensure that it is just brought to boiling point and then cooled. (*Tropical Medicine*—Rogers & Megaw, 1935).

REPORT OF EXPERT COMMITTEE ON NUTRITION

The first part of the report states that 2,400 calories net a day are adequate for an adult man or woman living an ordinary everyday life in a temperate climate and not engaged in manual work. This allowance is to be supplemented for various grades of muscular activity. For light work it is estimated that an additional 50 calories per hour of work is needed; for moderate work, 50 to 100 calories; for hard work, 100 to 200 calories, for very hard work, 200 calories or more. For pregnant women 2,400 calories are considered sufficient, and for nursing mothers 3,000. For infants energy requirements are assessed on the basis of 100 calories per kilo. of body weight for the first three months of life; 90 calories from three to six months; 80 to 90 calories for six to twelve months. Further, it is suggested that the activities of girls from the age of 7 upwards and of boys from 7 to 11 years should be looked on as equivalent to light work; and those of boys from 11 to 18 years as equivalent to moderate work. As a general recommendation it is suggested that the protein intake of adult should not fall below 1 gm. of protein per kilo. of body weight, and that a part of this should be from animal sources. Some animal protein is considered essential during growth, pregnancy, and lactation. In the second part of the report, on mineral and vitamin requirements, the committee states that the most important protective foods are milk and milk products, eggs, and glandular tissues; then come green leaf vegetables, fruit, fat fish, and meat. It is also pointed out that "the increasing habit of large sugar consumption tends to lessen the amount of protective foods in the diet and is to be regarded with concern." In an attempt to define the quantitative needs of protective foods for the pregnant and nursing woman, the committee stresses the difficulty of arranging such a diet as will provide calcium, phosphorus, iron and vitamins B₁, B₂, C, and D. In this respect milk and eggs are of great service; the former rich in calcium, phosphates, and vitamin B₂; the latter containing vitamins A, B₁, B₂ and D, and being rich in iron. The proteins of both are of high nutritive value. It is recommended that additional vitamin D, in the form of cod-liver oil, should be given to the growing child and to the mother. It is also suggested that potatoes should replace part of the sugar and milled cereals in the diet, for they are a source of vitamin C, and yield more iron, calcium, phosphorus, and the B vitamins. On general lines the committee is of opinion that, (i) variety in diet tends to safety, so long as there is a sufficiency of

'protective, foods; (ii) that lightly milled cereals and potatoes should partly replace white flour (excessive consumption of sugar is condemned); (iii) that more milk should be taken at all ages, and that the nutritive value of skimmed and separated milk should be more widely appreciated; (iv) that fresh fruit and vegetables should always be included in a normal mixed diet; (v) that extra vitamin D should be provided, 'wherever sunshine is not abundant' and that the other vitamins are adequately provided in a diet which contains optimum amounts of protective foods. (*Brit. Med. Jour.* 1935, p. 1215).

LOW VOLTAGE X-RAY THERAPY

During recent years one of the most interesting developments of radiation therapy has been the use of higher and higher voltages in X-ray treatment and at the same time a parallel development has taken place in the field of relatively low voltages of the order of 50 kV. The dosage may now be measured and accurately controlled in a way previously impossible, so that even the very high dosage rates now available present little danger or difficulty in the handling. It is chiefly the work of Chaoul which has led to the experimental investigations regards the use of X-ray tubes at small focal skin distances with considerable success. The X-rays are generated at a constant voltage of approximately 60 kV, with 4 mA tube current. The tube is so designed as to have the source of radiation at one end of an earthed metal tube, the rays emerging through the target of gold-plated nickel and the water-cooling jacket. These normally constitute the sole filters employed, in all equivalent to approximately 0.2 mm. nickel. The mean wave length is roughly 0.32 Å. U. The field on the irradiated skin is limited by metal applicators slipped on to the end of the tube, these applicators also ensuring the focal skin distance desired. The latter is usually 5 cm. or 3 cm., while the applicator may be either circular or elongated according to the lesion to be treated. Applicators of special shapes and sizes can be easily constructed. The dosage rate in air at 5 cm. focal skin distance, 60 kV and 4 mA, is approximately 110 r/min., while with "back scatter" this normally increases to about 130 r/min. All doses are defined with back scatter. This dosage rate is approximately twenty-five times that obtained from a 1-gm. radium 'bomb' at the same focal skin distance.

The daily dose per field used by Chaoul is 400 r with back scatter. The total dose per field is not arbitrarily selected, but depends somewhat on the reaction of the lesion to treatment. Usually, by about the fourth day the skin immediately surrounding the lesion, and purposely included in the field, has developed a mild degree of erythema, while during the next few days a pigmentation often occurs. The extent of both erythema and pigmentation depends very markedly on the usual factors, such as region of the body, condition of the skin, vascularity of the subcutaneous stratum, coloration of the patient, etc.

The edge of the erythematous area is very sharply marked, corresponding to the rim of the applicator, and although measurement shows often a 40 per cent. difference between the dose received at the centre of the field and that at the edge, the skin reaction appears quite uniform over the whole area. Regression of the lesion is occasionally noticeable even by the third day.

The total dosage is usually 5,000 to 6,000 r per field spread over about fifteen days, but irradiation up to this limit is continued until the erythema is well developed. The resulting skin reaction appears similar in all respects to that following radium treatment, with the exception of a shorter period of development. After intense irradiation skin sloughing results, but epithelialization rapidly proceeds from the periphery to cover the area with a pale scar. The sharply localised action of the beam renders the patient free from constitutional after-effects, so that a number of areas may be treated at one session, limited only by such factors as time and convenience. Even as many as six separate fields require only about twenty minutes to complete, the 400 r per field being obtained in about three minutes.

INDICATIONS. The following types of cases readily (according to Chaoul) admit of treatment by such low voltage therapy. *Skin cancer*, such as rodent ulcer and epitheliomata. *Buccal cancer*. This comprises squamous epitheliomata of lips, floor of mouth, alveolus, tongue, cheek, palate and tonsil pharynx. *Mammary cancer*. *Cancer of the cervix*. *Deep-seated lesions*. (*Brit. Med. Jour.*, Oct. 26, 1935).

OXYGEN THERAPY

It would hardly be an exaggeration to say that the methods of oxygen administration generally used have been so ineffective as to reduce this form of therapy to little more than a pious gesture. Much wider use has been made of oxygen therapy in America. This is reflected in the commercial production of several varieties of oxygen tent apparatus, and of special aids for nasal catheter administration of oxygen; and in the provision of oxygen chambers in many large American hospitals.

Of these three effective and clinical applicable methods, the oxygen chamber would naturally be expected to be the most effective, when available. The initial and upkeep costs of such a chamber are high, and it can obviously be available only in a large hospital. The nasal catheter method has the advantage of cheapness and ready availability. It is reasonably efficient if the tip of the catheter be introduced as far as the oropharynx and an adequate flow of oxygen maintained. Barach and Baker *et al* have shown that a flow of 5 litres per minute will maintain an effective concentration of about 35 per cent., even with a raised respiration rate. The catheter should have several perforations near its tip and the oxygen must be passed through warm

water to avoid painful desiccation of the pharyngeal mucosa. Several combined-flow-meter and humidifier devices are commercially available in America. There is no doubt, that oxygen can be more efficiently administered by a properly designed tent than by the best nasal catheter device. Finality has by no means been attained in tent design, as a survey of the various designs available will show; and it is possible that with increasing experience, useful modifications will increase the clinical usefulness of these devices. At present, the chief difficulty is the fact that enclosure in the apparatus often seems to have an unfavourable psychological effect on the patient. In the experience of some hospitals this sensation is so intense that a patient can hardly be induced to remain in it. A minor, but real, addition to this difficulty in the past was the unpleasant smell of rubber which tends to emanate especially from a new tent, this may well be eliminated in the most modern tents. Finally the nursing of a patient in the tent is undoubtedly a difficult problem. Favourable results following the use of their tent in treatment of a variety of pulmonary and cardiac conditions have been reviewed by Argyll Campbell and Poulton in their recent book. The available data on Oxygen and Carbon Dioxide Therapy suggest that the tent has been of more value in broncho- than in lobar pneumonia. This finding is in accord with theoretical considerations based on the pathology of these two forms of pneumonia. In cardiac failure it appears that more improvement is observed in cases of failure due to arterio-sclerotic disease than in those due to rheumatic disease. In cases of congestive cardiac failure reacting favourably to prolonged oxygen therapy, relief of dyspnoea and diminution of anoxaemia are almost immediate, and a fall of venous pressure, accompanied by diuresis is observed. In England favourable results of treatment in Dr. Poulton's tent have been recorded in cases of bronchitis and emphysema with circulatory failure, cyanosis after pulmonary lobectomy, and broncho-pneumonia complicating whooping cough. In very young infants the psychological troubles do not of course arise, and it is of interest that some of the most favourable results in pneumonia have been observed in infants. After such serious thoracic operations as lobectomy or thoracoplasty, the patient has to be content not only with shock but also with a local injury to the respiratory bellows; and in these cases the use of the tent in the first few days after operation may well save life.

There has been a tendency to pay insufficient attention to the late results in oxygen therapy. If these are considered it becomes apparent that it is in such conditions as the immediate post-operative period in major thoracic surgery, and in the pneumonia of infants, that the treatment is likely to be most efficacious, judged by the criterion of permanent restoration to useful life. Temporary improvement undoubtedly follows in some cases of chronic disease, such as arterio-sclerotic heart failure and pulmonary fibrosis, but cannot be expected to be maintained on return to normal atmosphere. In London the tent may prove espe-

cially useful during fogs, not only providing a high concentration of oxygen but also acting as a local air-conditioning plant. In an investigation dealing with patients ill enough to require oxygen administration for relief of anoxæmia, it is well-nigh impossible to provide satisfactory controls. It is greatly to be hoped, therefore, that the combined experience of clinicians in the London teaching hospitals with the oxygen tents rendered available by the British Red Cross Society will provide a basis for a reasoned appraisal of the value of this method of treatment. (*Lancet*, 1935, Vol. 2, No. 24).

PREMEDICATION

Pre-Anæsthetic Drugs

Nervous and highly-strung patients, especially children, should receive some form of sedative drug treatment to ameliorate the psychic effect before operation. Premedicants greatly decrease the amount of general anæsthetic needed subsequently. Such drugs should be carefully selected. The old and common practice of administering morphine to patients as a preliminary to chloroform anæsthesia has been given up and lately a number of premedicant drugs have come into use.

DRUGS GIVEN BY THE MOUTH. (a) *Chloretone*. Chloretone in doses of 0.65 to 0.97 gm. (10 to 15 gr.) has largely been used as a routine measure before ether anæsthesia. The advantages are many, the patient is brought to the operation theatre asleep and the post-anæsthetic vomiting is very much reduced. (b) *The barbiturates* (sodium amytal and nembutal). These drugs should be given in large doses so as to ensure that the patient is asleep before the general anæsthetic is begun. The use of sodium amytal should be restricted to robust and virile patients and is given in divided doses; 3 gr. the night before operation, 3 gr. three hours before, and 6 gr. two hours before the operation. The drawbacks to the use of these drugs are a fall of blood pressure and very often a period of excitement which can be controlled by morphine, follows. Nembutal is considered to be a safer drug than sodium amytal, but its sedative effect is much less potent and its action is very variable. The drug is suitable for women and the less vigorous male patients. It should be given in 3 gr. doses half an hour before operation. The custom of combining morphine with the barbiturates is not sound and should be discarded. Pernoxon, sodium alurate, pernoston, and other barbiturates are not very popular.

DRUGS GIVEN INTRAVENOUSLY AND SUBCUTANEOUSLY. (a) *The barbiturates*. Undesirable effects such as the fall of blood pressure, idiosyncrasy, etc., have led the anæsthetists to give up the intravenous use of the barbiturates in favour of their oral administration. Sodium evipan has won the reputation of a potent drug, producing a degree of narcosis equivalent to the third stage of anæsthesia. The fall of blood pressure is however, sometimes marked.

(b) *Morphine and its derivatives.* The use of morphine is now becoming much less frequent as it is a respiratory depressant and increases the post-anæsthetic vomiting. For obvious reasons the combined administration of hyoscine and morphine should never be encouraged.

DRUGS ADMINISTERED PER RECTUM. Such administration of drugs is preferred because in nervous and frightened patients the absorption of premedicants from the stomach is inhibited. Paraldehyde and avertin are the best narcotics for use in this way.

Paraldehyde. It is given in doses up to 0.56 c.cm. per kilo. (1 dr. per stone) of body weight. One part of paraldehyde is shaken up with ten parts of water and injected one hour before operation. The time of narcosis varies in different patients and small hæmorrhages in the mucous coat of the stomach, indicated by coffee-ground vomit, have occasionally been met with.

Avertin. It is considered the most suitable premedicant in small doses and is given in proportion to the age, physical condition, and weight of the patient. The usual dose is from 0.05 to 0.1 c.cm. per kilo. body weight. The fall of blood pressure is negligible, the patient falls asleep within half an hour of the injection and very little general anæsthetic is necessary to maintain narcosis.

Even in the administration of gas and oxygen some form of premedication is essential. Where post-anæsthetic vomiting is not desirable the preliminary administration of a small dose of avertin followed by anaesthesia with nitrous oxide and oxygen is very satisfactory.

Though a very old remedy, atropine has been admitted to be one of the best premedicant drug as it can be used before general anæsthetic. It inhibits the action of the vagus and diminishes mucous secretion. It should be given hypodermically in doses of 1/200 to 1/150 gr. one hour before operation except in the case of children, when it is better to give tincture of belladonna by the mouth, to obviate the discomfort of the subcutaneous injection. High basal metabolic rate is a contraindication to its use. (*Brit. Med. Jour.*, 1935, p. 782).

DIGITALOIDS (p. 246)

The effect of digitalis when given by mouth is decreased as a result of its reaction with the acid gastric juice and the intestinal alkali. Absorption is inhibited owing to the surface activity and adsorption of the drug. The effects become progressively decreased in patients under the pathological conditions of circulatory failure. With oral administration, even when pure substances are used, the production of quantitatively predetermined effects becomes impossible. By the rectal route these sources of error, although diminished, are not entirely removed, and the local irritative effects produced by digitalis glucosides exclude intramuscular and subcutaneous injections in their therapy. The only suitable way of administering this valuable remedy quantitatively to

the heart is, therefore, by intravenous injection. The essential conditions for intravenous administration of a drug are solubility in water and the stability of the watery solution. Recent developments in the chemistry of digitalis have revealed close relationships between the different glucosides and this 'Digitalis monotonic', to use Straub's expression, explains to some extent the similarity of their pharmacological actions. All these glucosides can be split by hydrolysis into a sugar-free organic compound—the genin—and one or more carbohydrate molecules. The similarity in chemical constitution is confined, however, to genins. Greater difference occurs however in the structure of the sugars with which the genins are combined. The genins of the glucosides of *D. purpurea* (glucosides of the first order) are combined with 2 or 3 molecules of digitoxose—a methyl pentose which occurs only in plants and which can be broken down by the human organism only with difficulty. On the other hand sugars of the digitaloids (glucosides of the second order, such as strophanthin, adonis, scilla, etc.) are easily decomposed in the animal organism since they are for the most part pentoses and hexoses. The carbohydrate of K-strophanthin, for instance, is a disaccharide consisting of glucose and cymarose both of which are readily soluble in water. G-strophanthin or ouabain contains the methyl pentose rhamnose which is far less soluble in water.

Slowing of the pulse rate being chosen as the criterion of action, the effect of glucosides of the first order was found to occur more slowly and to last longer than that of the glucosides of the second order. In the case of the latter the action both appeared and disappeared rapidly and, in contrast with what is found with digitoxin, the action could be maintained by repeated injections without any toxic effects attributable to cumulation of the drug appearing. Cumulation therefore proved to be least with the digitaloids and the absence of this phenomenon is an essential condition for the successful development of the intravenous method in treatment with the glucosides.

The narrowed choice among the digitaloids now fell on that group in which not the diuretic action, as in the case of adonis and scilla, but the cardiac action preponderated. K-strophanthin serves the purpose since it proved to be less toxic and more easily soluble than G-strophanthin. The toxic range of concentration is more readily attained under these conditions with digitoxin than with strophanthin. Therapeutic doses of the glucoside increased the isolated heart's capacity for work and its period of survival, and inhibited the processes of fatigue; and on the other hand, that toxic doses, themselves leading to morphological changes in the muscle, decreased the capacity for work and accelerated the processes of fatigue. Experimental investigations have shown that the digitaloids and especially the strophanthins are fixed to the heart for so short a period that the therapeutic dose is eliminated within 24 hours. Amongst the strophanthins the crystalline

product from G-strophanthin is more toxic than the amorphous compound obtained from K-strophanthin.

The main effect of digitalis in heart failure is an increase in the stroke volume and a change in the distribution of blood, resulting from the increased circulation rate. The intravenous injection of the glucosides is followed by the fixation of about 10 per cent. of the dose by the heart.

The absence of appreciable effect on the healthy as also on the diseased heart when functionally compensated and its appearance after minute doses in decompensation, may perhaps be explained in part by the intramuscular development of a specific sensitivity to digitalis in this latter group. The amount of strophanthin fixed per gramme of heart muscle has been calculated by Clark (1 gm. adsorbs at most 0.0002 mg. of the drug. One-tenth of the lethal dose of the drug has a detectable effect upon the diseased heart exhibiting a high sensitivity to digitalis, the concentration in which digitalis acts is of the same order as that found in the case of the hormones. The question whether there arises a specific increase in sensitivity to digitalis when the heart fails is controversial. The measurement of body weight excludes the possibility of neglecting the extrarenal loss of water and indicates by direct means the day on which the removal of oedema fluid is complete and to the time when the minute volume of fluid has in all probability reached its optimum. This enables one to avoid overdosage and at the same time, by gradation of the dose within 0.1 gm., to control accurately the rate of fluid removal and so to delimit precisely the period allowed for complete elimination of the retained water; a realisation of therapeutic ideal of obtaining optimal effects from the smallest doses. (*Lancet*, 1935, Vol. 2, p. 1101).

PHYSIOLOGY OF HYPERPYREXIA PRODUCED BY ARTIFICIAL MEANS

Is fever produced by diathermy and physical means the same as fever occurring from infections? The answer is in the negative. From the strictly physiological standpoint, the great majority of evidence points towards the two being entirely different, with the exception of temperature or heat, which they both share in common. To be sure, there are some findings, for example, in the urine and sweat, which are similar, or possibly synonymous, and the clinical interpretation of conditions and results add further to this conception, but this discussion is concerned only with the physiology. Von Grafe deals a vital blow when he shows evidence that most of the metabolic changes can be duplicated with infection devoid of and divorced from fever. The Juaregg school in general is very staunch in its opinion that something in addition to heat is responsible for the results in treating central nervous system syphilis, since in many cases better results have

been obtained with malaria at temperatures of 102°F. than with typhoid and other methods at much higher levels. There is a marked increase in basal metabolism in artificial fever, and possibly much of the benefit comes solely through this source, since its application is nearly always in diseases which at that time are not running temperatures of their own accord. That bacteria and infectious agents are actually destroyed is evident, but still may be questioned. Possibly the increased metabolism and circulation alone, hastening absorption and elimination of their by-products can be just as important a factors. In the face of current clinical reports carrying with them so much evidence of therapeutic benefit, physiological lack of support should not be permitted to hamper or stop continued progress and use of the measure in general except in that it must involve safety to the patient.

The conclusions are:—(1) From the physiological point of view, hyperpyrexia produced by physical means is not synonymous with spontaneous fever produced by disease. (2) Hyperpyrexia induced by malaria, chemicals, foreign proteins, etc. is also different from that produced by physical means. (3) The role played by heat retention in combating disease might share a common denominator in all three types of fever. (4) The heart rate is subject to changes in skin temperature more definitely than to changes in body temperature. (*Med. Press and Circular*, 1935, Vol. 191).

NON-SPECIFIC PROTEIN THERAPY (p. 1418)

(1) *Milk*. Ordinary skimmed milk, either fresh or pasteurized, is boiled for from five to ten minutes and then cooled to body temperature. The first dose for adults is 5 c.cm. injected intramuscularly, usually into the gluteal muscles. The dose is increased 2 or 3 c.cm. with each injection until a maximum of from 10 to 15 c.cm. is reached. (2) *Diphtheria antitoxin*. As used for foreign protein therapy, diphtheria antitoxin is not given for its antitoxic property but because it is an available form of horse serum. The dose is not fixed but is usually from 2 to 4 c.cm. given intramuscularly. In doses of this size it will usually induce a temperature of from 100° to 101°F. (3) *Vaccines*. Ordinary stock and autogenous vaccines are given intramuscularly unless sharp thermal reactions are desired. When such is the case, typhoid vaccine is by far the most popular agent and is given intravenously. Intravenous injections of Gram positive bacteria such as the streptococcus, pneumococcus and staphylococcus are much less likely to cause febrile reactions than the Gram negative organisms such as the gonococcus and typhoid bacillus. The reason for this difference is not clear.

REACTION. The reaction to foreign protein injections varies from an almost imperceptible one to extreme shock associated with high fever, profound vasomotor disturbance and other constitutional pheno-

mena. The reaction depends on the substance injected, the dose employed and the method of administration. It also depends a great deal on the physical condition of the patient and the number of previous injections. Intramuscular injections of protein usually excite only focal reaction, that is, a temporary flare up of acute symptoms in some focus of infection; a constitutional reaction may be entirely absent. When foreign proteins are given intravenously, the reactions are sharper and make their appearance more promptly. In acute infections, such as typhoid or pneumonia, in which a temperature of 102° to 104°F. already exists, the temperature during a protein reaction may sometimes go to 106° or 107°F. For this reason the dose of protein or vaccine should be very carefully gauged in the treatment of febrile conditions. As a rule the dosage for a febrile patient should be about half that for afebrile individuals.

Mechanism of the reaction. The typical thermal reaction of protein fever can be divided roughly into three phases. Immediately after the intravenous injection there is a short prodromal period, which is characterized by first a stage of latency with no symptoms and later a stage of chill. Then the temperature begins to rise. The period from the onset of fever to the point of maximum temperature is referred to as the first or *negative* phase. The second or *positive* phase extends from the height of the fever to the return of normal temperature. The physiological changes that take place in the body during the protein reaction are: (1) Alteration in the basal metabolism. (2) Peripheral and splanchnic vasomotor changes, including alterations in blood pressure and in the calibre and permeability of the arterioles and capillaries. (3) Alterations in renal function, detectable in the output and in the acidity of the urine, excretion of phenolsulphonphthalein, and concentration of nitrogen, phosphate, urea, uric acid, allantoin and albumin. (4) Alterations in serum ferments, antiferments, antibodies and the Wassermann reaction. (5) Alterations in organic activity demonstrated by increased secretion of lymph, bile, saliva, breast milk and menstrual flow and by changes in the activity of the liver, gastro-intestinal tract and spleen. (6) Alterations in the volume, specific gravity, freezing point and viscosity of the blood. (7) Alterations in the cellular elements of the blood. (8) Alterations in the fragility of the blood platelets and in fibrinogen, thrombokinase, coagulation time and sedimentation rate. (9) Alterations in the chemical constituents of the blood demonstrated by changes in the carbon dioxide tension of the plasma, carbon dioxide combining power, total non-protein nitrogen of whole blood and of serum, sugar tolerance, albumin globulin ratio and concentration of urea, uric acid, sugar, fat, total serum protein and chlorides. Jobling and Peterson attached great importance to the mobilization of enzymes, particularly proteases and lipases, following the injection of proteins. Perhaps the most important function of the foreign protein reaction is the mobilization of immune bodies in the circulating blood.

Untoward reactions. Severe and even fatal reactions sometimes follow the intravenous injection of foreign protein. Such occurrences, however, usually take place in patients who are already seriously ill or who have been greatly overdosed with protein. There have been surprisingly few severe anaphylactic reactions. The complications attributed to foreign protein reactions have been delirium tremens, cardiac failure, vascular thromboses, acute nephritis, herpes labialis, rheumatic purpura, acute diarrhoea, and activation of old pulmonary tuberculosis.

Clinical Application of Protein Therapy. Typhoid. Typhoid was the first infectious disease to be treated by foreign protein therapy. Holler used small doses of a 10 per cent. solution of deutoalbumose, beginning with two treatments a day and later giving one treatment daily continuing the injections until the fever was broken.

Pneumonia. Pneumonia is a disease for which an efficacious serum therapy is available in more than 60 per cent. of the cases. There still remains 40 per cent. of pneumococcic pneumonias in which some other form of specific or non-specific treatment would be feasible. In an infection of such comparatively short duration as pneumonia the interpretation of the results of protein therapy would be difficult unless the injections were given very early in the disease.

Nervous diseases. Both relapsing fever and rat-bite fever have been used therapeutically in dementia paralytica. The results with relapsing fever as reported by Plant and Steiner and more recently by Signorelli seem to be about as good as those obtained by others with malaria; this is still further evidence that it is the febrile reaction and not the agent which produced the fever which is the essential part of the treatment. In 1924 Grosz reported very favourably on the treatment of multiple sclerosis with foreign protein therapy. Such cases were treated with typhoid vaccine and with malaria.

Diseases of the skin. In dermatology, foreign protein therapy has been widely used, and with considerable success, in certain inflammatory conditions, such as furunculosis, carbuncle and other staphylococcic infection of the skin, and to a less extent in ringworm, lupus, pruritus and the like. Sometimes a persistent form of urticaria will yield promptly to boiled milk or to some form of bacterial vaccine. Especially good results have been claimed for colon bacillus vaccine in urticaria. O'Leary has found foreign protein most beneficial in the treatment of anthrax and erysipelas. Schmidt reports excellent results with milk therapy in erysipelas.

Diseases of the eye. Non-specific therapy in the form of boiled milk or typhoid vaccine has been employed extensively in iritis, uveitis, keratitis, conjunctivitis and other inflammatory conditions of the eye. There seems to be some disagreement as to the benefit to be derived from protein therapy in trachoma.

Gynaecology. In pelvic diseases the most important field of protein therapy has been in adnexal infections of an acute or subacute type. In such conditions the results of protein therapy have often been quite striking. The consensus of opinion is, however, that its chief function is in the relief of pain and extreme tenderness. There is considerable doubt as to just how often a tubal infection is 'cured' by protein therapy. For gonococcic infections however, fever therapy is now more successfully used, in the form of diathermy or the short wave than by typhoid or gonococcus vaccine.

Peptic ulcer. One would hardly expect protein therapy to have any value in the treatment of peptic ulcer. Prilram, however, has reported a large series of ulcers treated by intravenous injections of a vegetable albumin (novoprotein) and states that the pain was much relieved in from 50 to 60 per cent. of the cases. He even goes so far as to assert that roentgen observations indicate healing of the ulcer. Treatments were given at intervals of from two to four days, the patient receiving a total of eight or ten injections.

Vascular disease. One of the newer fields for foreign protein therapy is that of vascular disease, particularly thrombo-angitis obliterans. In vascular disease, however, it is probably the vasodilatation rather than the fever, leucocytosis or mobilization of immune bodies that is responsible for the beneficial effect obtained. According to Wright, the desired physiologic effect of fever therapy in vascular disease is release of spasm of the partially occluded vessels with resulting increase in the local capillary circulation. This is followed by cessation of pain and healing of ulcerations, if they exist.

Contraindications. The more important contraindications to intravenous foreign protein therapy are: (1) Advanced arterial, renal or cardiac disease. Patients with cardiac decompensation should not have intravenous protein therapy. On the other hand, rheumatic endocarditis with good compensation is not a contraindication. (2) Allergic states or conditions of marked protein sensitivity, such as angioneurotic oedema, giant urticaria and the like. (3) States of extreme exhaustion following prolonged illness. (4) Pulmonary tuberculosis, active or quiescent. (5) Haemorrhagic conditions, such as hemophilia, bleeding ulcers, and the like. (6) Chronic alcoholism, for fear of delirium tremens. (7) Marked nervous sensibility as seen in hyperthyroidism and the like. (*Jour. Amer. Med. Assoc.*, 1935, Vol. 105, No. 23).

BIOLOGICAL PROBLEM IN CHEMOTHERAPY

The discovery of a technique by means of which trypanosomes may be kept alive *in vitro* for at least 24 hours has enabled certain chemotherapeutic problems to be reinvestigated. Trivalent arsenic and antimony compounds have in comparison with pentavalent compounds surprisingly high trypanocidal activity both *in vitro* and *in vivo*. This

suggests that the therapeutic action of the trivalent arsenicals and arspenamine compounds is dependent on the trypanocidal action of the unchanged drugs, while that of the pentavalent compounds is associated with some previous change, probably reduction, in the body of the host. Nevertheless pentavalent are preferred to trivalent compounds in the treatment of trypanosome infections. This is probably due to a number of factors. When trivalent arsenicals are injected into rabbits the serum is at once endowed with an enormous trypanocidal titre. This high titre does not, however, last long. When pentavalent compounds are injected the trypanocidal titre develops much more slowly. Trivalent arsenicals are also excreted more rapidly in the urine, while pentavalent compounds such as tryparsamide, though rapidly giving rise to a high trypanocidal titre in the urine, are much more slowly excreted. After an injection of tryparsamide into a rabbit, for instance, the trypanocidal titre of the urine only reaches zero after a day or more. A further difference between tri- and pentavalent arsenical compounds is that reduced tryparsamide and neoarsphenamine diffuse rapidly into and out of red blood corpuscles and are unchanged in the process. Tryparsamide also diffuses into red blood corpuscles but is to some extent reduced by the hæmoglobin into its highly trypanocidal trivalent form. Other tissues also probably play a part in this reduction.

The essential characteristic of drug resistance is found to be a change in the parasites whereby they do not fix the drug applied *in vitro* as do normal parasites. The development of a resistant strain is fundamentally a mutation, *i.e.*, a gradual change in all or certain individuals resulting from the stimulus of frequent exposures to suitable concentrations of drug. When once a strain of trypanosomes has become arsenic-resistant it retains the character indefinitely. It is not lost when passed by syringe nor by numerous cyclical transmissions through the natural intermediate host. The importance of this concept is seen in the fact that arsenic-resistant strains of trypanosomes are being obtained in considerable numbers from African natives, probably as a result of the wholesale atoxylyzation of patients which is now being carried out by itinerant medical missions. Although it is easy to produce strains of trypanosomes resistant to aromatic arsenicals and antimonials it is fortunately difficult to produce strains resistant to Bayer 205. Experiments are described to show the importance of the size, and spacing a number of doses of a drug in producing resistant strains. (*Trans. Roy. Soc. Trop. Med. & Hyg.* 1935, Vol. 28, No. 5).

SEX HORMONES IN PRACTICE

It is agreed that promiscuous administration of endocrine extracts is sometimes harmful and usually valueless; that they must be used only after careful exclusion of relevant organic lesions; and that the user needs a cautious understanding which can develop only from

knowledge of physiology. Admitting all this, it seems that more interest should be taken, here and now, in the rational treatment of the menstrual and reproductive disorders that incapacitate so many women.

Inadequate menstrual loss which may take the form of primary amenorrhœa in which a girl reaches adult life without having a menstrual period there are usually signs of gross ovarian deficiency, the most important of these being an under-developed uterus, perhaps no larger than a hazel-nut. Such an organ, infantile in structure, is incapable of normal function, and the first aim of treatment therefore is to promote its growth. Kaufmann has shown that this can sometimes be done by giving large doses of the ovarian hormone known as œstrin or folliculin (*e.g.*, 200,000 to 4,000,000 international units of crystalline œstrone). The next object is to induce growth of the kind of endometrium associated with normal menstrual bleeding. In an adult uterus this can almost always be done by giving the corpus luteum hormone, progesterin, in doses of 5 to 50 rabbit units. Assuming success in these two aims, the primary defect—ovarian deficiency—remains to be overcome; for the injection of ovarian extracts is merely substitutive treatment, and it is doubtful how far it can initiate spontaneous menstrual cycles. The fundamental object is to convert the infantile ovary into an adult ovary with normal function. In immature animals this can be done by injecting gonadotropic (gonad-stimulating) principles derived either directly from the pituitary gland or from urine excreted in pregnancy. It would therefore be reasonable in primary amenorrhœa to follow treatment of the uterus (with œstrin and progesterin) by administration of gonadotropic extracts; and there is in fact evidence that in a few cases this has led to the onset of cyclical menstruation. It has to be acknowledged that the extracts at present in use are seldom potent enough to produce any lasting effect on a seriously undeveloped ovary. But where the deficiency is of secondary amenorrhœa, treatment is more promising; and in oligomenorrhœa, so often associated with dysmenorrhœa or sterility the outlook is far more hopeful. The principles of treatment here are much the same, but some authorities such as Clauberg claim that œstrin by itself suffices for cure. He finds that in immature mice its injection may actually lead to the formation of corpora lutea, and since it is well established that œstrin has no direct action on the ovary this effect must, it seems, be due to stimulation of the pituitary. It has become evident that the ovary and anterior pituitary are complementary in action; too much œstrin depresses pituitary activity while too little makes it unusually apparent. Clauberg describes this as the '*pituitary release phenomenon*'; he believes that large doses of œstrin promote pituitary quiescence and that sudden cessation of them brings about abnormal pituitary activity sufficient to cause formation of corpora lutea in the ovary and consequent changes in the uterine endometrium leading to pregnancy. The dysmenorrhœa often associated with scantiness of

menstruation responds, it is said, to oestrin therapy in some 30 to 50 per cent. of cases.

There are two other important conditions in which treatment with ovarian hormones is especially satisfactory. First, oestrin is found useful—in less heroic doses, and even by mouth—at the menopause. Hot flushes sometimes yield readily to relatively small doses such as 500 to 3,000 international units of oestrone daily by mouth. Treatment induces a sense of well-being and may relieve associated disorders such as pruritus or kraurosis vulvae and acne rosacea. Secondly, progestin finds rational employment in cases where repeated abortion in early pregnancy has no apparent cause, and the proportion of successful results is too high to be fortuitous. (*Lancet.*, 1935, Vol. 2, p. 1467).

TRYPANOCIDAL ACTION OF NORMAL HUMAN SERUM

The normal serum of man will destroy the trypanosomes pathogenic for animals (*e.g.*, *T. brucei*, *T. equiperdum*, *T. equinum*, etc.) either in the test tube or in the body of rodents infected with these parasites. Human serum does not affect the trypanosomes pathogenic for man (*T. gambiense*, *T. rhodesiense* or *T. Cruzi*), the common trypanosome of rats (*T. Lewisi*) or a trypanosome of newts (*T. diemyctyli*). One of the human trypanosomes, *T. rhodesiense*, is distinctive in that it becomes susceptible to the action of human serum after it has been passed successively through mice. The serum of no other animals, excepting certain monkeys, manifests trypanocidal activity. The serum of some monkeys, however, *e.g.*, that of the baboon, destroys not only the trypanosomes pathogenic for the lower animals but, as well, those infective for man.

The trypanocidal substance of human serum is found in the globulin fraction of the serum. It is thermolabile, being destroyed wholly when the serum is heated at 64°C. for an hour, and being reduced rapidly when the serum is let stand at room temperature. The trypanocidal substance passes readily through Berkefeld filters and with diminished intensity through collodion ultrafilters. It is removed from serum by absorption with trypanosomes or bacteria (the typhoid bacillus; *Proteus*). The substance exhibits its activity independently of all the known components of alexin. The essential substance in the human serum which brings about the trypanocidal effect is antigenic, and a specific anti-trypanocidal antibody develops in rabbits repeatedly treated with an active serum.

The trypanocidal substance probably originates in the normally functioning healthy liver. It is found in the blood serum and in serous exudates. The cerebrospinal fluid and the urine are without trypanocidal power. The substance appears in infants at a very early age and may be present at birth. It is probably elaborated within the body of the young child, since it is found neither to pass the placenta nor to

occur in human milk. The trypanocidal power is enhanced in women late in the period of gestation and is maintained at a high level for some time after delivery.

It seems unlikely that the action of the trypanocidal substance is that of an opsonin or an agglutinin, and the property is manifested wholly without the intervention of alexin. Some investigators have felt it acts essentially as a chemotherapeutic substance. Susceptible strains of trypanosomes become resistant or fast to human serum after repeated exposure to the serum in a manner comparable to that in which they become resistant or fast to drugs.

Since human serum affects only those species of trypanosomes which are pathogenic for animals and which are non-infective for man, and is without effect on the trypanosomes which are infective for man, it is by some believed that the trypanocidal action of serum is responsible for man's immunity to the animal pathogens. It is known, however, that strains of animal trypanosomes which have been rendered serum-fast still are non-infective for man, and that strains of human trypanosomes (*T. rhodesiense*) which become susceptible to human serum after repeated passage through animals retain their infectivity for man. Furthermore, the serum-resistant parasite *T. Lewisi*, which is widespread among rats is apparently unable to infect man. The serum of patients with trypanosomiasis is as active in trypanocidal power as that of normal persons. It appears, therefore, that the immunity of man to the animal trypanosomes depends on factors other than the trypanocidal activity of the serum.

The trypanocidal activity of human serum is sharply reduced in diseases which cause extensive destruction of the parenchyma of the liver. The fact that both the trypanocidal and bactericidal substances are removed from the serum by absorption with either trypanosomes or bacteria points toward a close similarity between the trypanocidal and bactericidal powers. The trypanocidal activity, however, differs from the bactericidal property and resembles the virus-neutralizing function of human serum in being limited to the serum of man and a few closely related primates and in occurring without the presence of alexin. (*Archives of Pathology*, 1935, Vol. 20, p. 788).

APPENDIX II

Appendix II contains general informations likely to be useful to the general practitioners in the Tropics.

TABLE OF BACTERIA PATHOGENIC TO MAN

WITH SPECIAL REFERENCE TO THE TROPICS

Disease	Common Name	Modern Nomenclature
Acne	White staphylococcus Orange staphylococcus Acne bacillus	Staphylococcus albus Staphylococcus aureus Corynebacterium acne
Actinomycosis	Actinomycetes bovis	Actinomycetes bovis
Adenitis	Streptococcus pyogenes Streptococcus scarlatinae	Streptococcus pyogenes Streptococcus scarlatinae
Adenitis (tuberculous)	Tubercle bacillus	Mycobacterium tuberculosis
Angina (Ludwig's)	Streptococcus hæmolyticus	Streptococcus pyogenes
Angina (Vincent's)	Staphylococcus Bacillus fusiformis	Staphylococcus Fusiformis fusiformis
Anthrax	Vincent's spirochaeta	Borrelia vincenti
Appendicitis	Anthrax bacillus Bacillus aerogenes capsulatus Bacillus fragilis Bacillus ramosus Bacillus fusiformis Bacillus fallax Bacillus oedematis maligni	Bacillus anthracis Clostridium welchii Fusiformis fragilis Fusiformis ramosus Fusiformis fusiformis Clostridium fallax Clostridium septicum
Arthritis	Streptococcus Colon bacillus Streptococcus viridans Orange staphylococcus Gonococcus Tubercle bacillus	Streptococcus anærobicus Escherichia coli (Bact. coli) Streptococcus viridans Staphylococcus aureus Neisseria gonorrhoeæ Mycobacterium tuberculosis

	Pneumococcus	Diplococcus pneumoniae (streptococcus pneumoniae)
Boil	Pyogenic organisms	Staphylococcus aureus
Botulism	Orange staphylococcus	Clostridium botulinum
Bronchitis	Bacillus botulinus	Staphylococcus aureus
	Orange staphylococcus	Gaffky tetragenus (M. tetragenus)
	Micrococcus tetragenus	Streptococcus pyogenes
	Hæmolytic streptococcus	Diplococcus pneumoniae (streptococcus pneumoniae)
	Pneumococcus	Neisseria catarrhalis
	Micrococcus catarrhalis	Klebsiella pneumoniae (Bact pneumoniae)
	Pneumobacillus	Actinomyces gedanensis
	Actinomyces gedanensis	Staphylococcus aureus
Bronchopneumonia (lobular pneumonia)...	Staphylococcus aureus	Streptococcus pyogenes
	Hæmolytic streptococcus	Bacterium pneumoniae
	Bacillus mucosus capsulatus	Actinomyces actinoides
	Bacillus actinoides	Hæmophilus influenzae
	Influenza bacillus	Pasteurella pestis
	Plague bacillus	Staphylococcus aureus
Carbuncle	Orange staphylococcus	Streptococcus pyogenes
Cellulitis	Hæmolytic streptococcus	Staphylococcus aureus
	Orange staphylococcus	Neisseria gonorrhoea
Cervicitis	Gonococcus	Staphylococcus aureus
	Orange staphylococcus	Streptococcus pyogenes
	Hæmolytic streptococcus	Escherichia coli (Bact. coli)
	Colon bacillus	Treponema pallidum
Chancre (hard)	Spirochaeta pallida	Hæmophilus ducreyii
Chancroid (soft chancre)	Ducrey's bacillus	Staphylococcus aureus
Cholecystitis	Orange staphylococcus	Escherichia coli (Bact. coli)
	Colon bacillus	Eberthella typhi (Bact. typhosum)
	Bacillus typhosus	Bact. paratyphosum
	Paratyphoid group	Streptococcus
	Streptococcus	Vibrio comma (Vibrio cholerae)
Cholera	Comma bacillus	

Disease	Common Name	Nomenclature
Conjunctivitis (acute) ...	Kock-Week bacillus	Haemophilus conjunctivitis
Conjunctivitis " (sub-acute or angular) ...	Pneumococcus	Diplococcus pneumoniae (Streptococcus pneumoniae)
Conjunctivitis (gonococcal) ...	Morax-Axenfeld bacillus	Haemophilus Morax-Axenfeld
Conjunctivitis (chronic) ...	Gonococcus	Neisseria gonorrhoeae
Cystitis ...	Bacillus xerosis	Corynebacterium xerosis
	Orange staphylococcus	Staphylococcus aureus
	Colon bacillus	Escherichia coli (Bact. coli)
	Bacillus proteus vulgaris	Proteus vulgaris
	Typhoid bacilli	Eberthella typhi (Bact. typhosum)
	Streptococcus faecalis	Streptococcus faecalis
	Bacillus pyocyaneus	Pseudomonas aeruginosa (Pseudomonas pyocyanea)
	Tubercle bacillus	Mycobacterium tuberculosis
	Bacillus enteritidis	Salmonella enteritidis (Bact. enteritidis)
Diarrhoea ...	Colon Bacillus	Escherichia coli (Bact. coli)
	Typhoid bacillus	Eberthella typhi (Bact. typhosum)
	Dysentery bacillus	Shigella dysenteriae (Bact. dysenteriae)
	Bacillus pyocyaneus	Pseudomonas aeruginosa (Pseudomonas pyocyanea)
Diphtheria ...	Diphtheria bacillus	Corynebacterium diphtheriae
Dysentery (bacillary) ...	Dysentery bacillus	Eberthella dysenteriae (Bact. dysenteriae)
	Dysentery bacillus (Shiga)	Bacterium shigae
	Dysentery bacillus (Flexner)	Eberthella paradysenteriae (Flexner) (Bact. flexneri)
	Paradysentery bacillus (Park)	Eberthella paradysenteriae (Park)
	Paradysentery bacillus (Hiss)	Eberthella paradysenteriae (Hiss)
	Bacillus dysenteriae (Sonne type)	Shigella paradysenteriae, var. Sonnei
	Bact. pseudo-carolinus	Bact. pseudo-carolinus

Eczema	...	White staphylococcus Streptococcus α & β	Staphylococcus albus Streptococcus α & β (Strepto. viridans & hæmolyticus)
Empyema	...	Orange staphylococcus Streptococcus viridans Pneumococcus	Staphylococcus aureus Streptococcus viridans Diplococcus pneumoniae (Strepto. pneumoniae)
Endocarditis	...	Tubercle bacillus Streptococcus hæmolyticus Streptococcus viridans Staphylococcus Pneumococcus	Mycobacterium tuberculosis Streptococcus pyogenes Streptococcus viridans • Staphylococcus Diplococcus pneumoniae (Streptococcus pneumoniae)
Endometritis	...	Gonococcus Staphylococcus pyogenes aureus β hæmolytic streptococcus Bacillus coli communior Bacillus proteus vulgaris Staphylococcus Gonococcus erysipelatis Tubercle bacillus Streptococcus erysipelatis Glanders bacillus	Neisseria gonorrhoeæ Staphylococcus aureus Streptococcus hæmolyticus Escherichia communior (Bact. communior) Proteus vulgaris Staphylococcus Neisseria gonorrhoeæ Mycobacterium tuberculosis Streptococcus erysipelatis Actinobacillus mallei
Epididymitis	...	Bacillus enteritidis Paratyphoid B Dysentery bacilli (Sonne) Staphylococcus Glanders bacillus Gonococcus Staphylococcus pyogenes aureus Hæmolytic streptococcus Bacillus coli communior Pneumococcus	Salmonella enteritidis (Bact. enteritidis) Bact. paratyphosum B Shigella paradyserteriae (Sonne) Staphylococcus aureus Actinobacillus mallei Neisseria gonorrhoeæ Staphylococcus aureus Streptococcus pyogenes Escherichia coli (Bact. coli) Diplococcus pneumoniae (Strepto. pneumoniae) Treponema pallidum
Erysipelas
Farcy
Food poisoning (bacterial)
Furunculosis
Glanders
Gonorrhoea
Hepatitis

Disease	Common Name	Modern Nomenclature
Impetigo	Streptococci (various types) Orange staphylococcus	Streptococcus hæmolyticus et viridans Staphylococcus aureus
*Influenza	Influenza bacillus (not accepted all) Pneumococcus (rarely) Hæmophilus influenzae Diplococcus pneumoniae (Streptococcus pneumoniae)
Iritis	Hæmolytic streptococcus Bacterium pneumosintes Spirochaeta pallida Tubercle bacillus Gonococcus Streptococcus pyogenes Dialister pneumosintes Treponema pallidum Mycobacterium tuberculosis Neisseria gonorrhoea
Jaundice (hæmorrhagic)	Streptococcus hæmolyticus Spirochaeta ictero-hæmorrhagiae	Streptococcus pyogenes Leptosira ictero-hæmorrhagiae
Laryngitis	White staphylococcus Streptococcus Pneumococcus	Staphylococcus albus Streptococcus Diplococcus pneumoniae (Streptococcus pneumoniae)
Leprosy	Leprosy bacillus	Mycobacterium leprae
Lobar pneumonia	Hæmolytic streptococcus Pneumococcus	Streptococcus pyogenes Diplococcus pneumoniae
Læpus vulgaris	Influenza bacillus	Hæmophilus influenzae
Lymphangitis	Tubercle bacillus Orange staphylococcus Hæmolytic streptococcus	Mycobacterium tuberculosis Staphylococcus aureus Streptococcus pyogenes
Madura Foot (Moccuma)	Actinomyces maduræ	Actinomyces maduræ
Malta fever	Bacillus melitensis Bacillus paramelitensis Bacillus abortus	Brucella melitensis Brucella paramelitensis Brucella abortus
Mastitis	Orange staphylococcus Hæmolytic streptococcus	Staphylococcus aureus Streptococcus pyogenes

Encephalitis Meningitis	Bacillus whitmori	Actinobacillus whitmori
	...	Meningococcus	Neisseria meningitidis
	...	Pneumococcus	Diplococcus pneumoniae (Strepto. pneumoniae)
Oöphoritis	Streptococcus pyogenes	Streptococcus pyogenes
	...	Orange staphylococcus	Staphylococcus aureus
	...	Tubercle bacillus	Mycobacterium tuberculosis
	...	Staphylococcus pyogenes albus	Staphylococcus albus
	...	Streptococcus erysipellatis	Streptococcus erysipellatis
Ophthalmia neonatorum Orchitis	...	Gonococcus	Neisseria gonorrhoeae
	...	Staphylococcus pyogenes albus	Staphylococcus albus
	...	Streptococcus	Streptococcus
Osteomyelitis	...	Gonococcus	Neisseria gonorrhoeae
	...	Staphylococcus pyogenes aureus	Staphylococcus aureus
	...	Streptococcus β	Streptococcus haemolyticus
	...	Typhoid bacillus	Eberthella typhi (Bact. typhosum)
	...	Tubercle bacillus	Mycobacterium tuberculosis
Otitis media	...	Streptococcus haemolyticus	Streptococcus pyogenes
	...	Pneumococcus	Diplococcus pneumoniae (Strepto. pneumoniae)
	...	Orange staphylococcus	Staphylococcus aureus
Ozaena Paratyphoid fever	...	Bacillus ozaenae	Klebsiella ozaenae
	...	Bacillus paratyphi A	Salmonella paratyphi (Bact. paratypho- sum A)
	...	Bacterium paratyphi B	Salmonella schottmulleri (Bact. paratypho- sum B)
Parotitis	Bacillus colambense	Salmonella columbensis (Bact. columbense)
	...	Staphylococcus pyogenes aureus	Staphylococcus aureus
	...	Streptococcus β	Streptococcus haemolyticus
Pemphigus	Micro-organisms of the mouth	
	...	Staphylococcus pyogenes albus	Staphylococcus albus
	...	Streptococcus haemolyticus II	Streptococcus haemolyticus II

*Recently a filtrable virus has been isolated.

Disease	Common Name	Modern Nomenclature
Pemphigus neonatorum	Orange staphylococcus	Staphylococcus aureus
Pericarditis	Staphylococcus	Staphylococcus
	Streptococcus	Streptococcus
	Pneumococcus	Diplococcus pneumoniae (Strepto. pneumoniae)
Pericystitis	Streptococcus	Streptococcus
	Typhoid bacillus	Eberthella typhi (Bact. typhosum)
	Bacillus paratyphi A	Salmonella paratyphi (Bact. paratyphosum A)
Peritonitis	Spirochaeta pallida	Treponema pallidum
	White staphylococcus	Staphylococcus albus
	Streptococcus	Streptococcus
	Pneumococcus	Diplococcus pneumoniae (Strepto. pneumoniae)
Pertussis (whooping cough)	Bacillus coli communior	Echerichia communior (Bact. communior)
	Pertussis bacillus	Haemophilus pertussis
Pharyngitis	Streptococcus haemolyticus	Streptococcus pyogenes
	Pneumococcus	Diplococcus pneumoniae (Strepto. pneumoniae)
Phlebitis	Micrococcus catarrhalis	Neisseria catarrhalis
Plague	Streptococcus pyogenes	Streptococcus pyogenes
Pleurisy	Plague bacillus	Pasteurella pestis
	Pneumococcus	Diplococcus pneumoniae (Streptococcus pneumoniae)
	Streptococcus	Streptococcus
	Staphylococcus	Staphylococcus
	Tubercle bacillus	Mycobacterium tuberculosis
	Bacillus typhosus	Eberthella typhi (Bact typhosum)
	Bacillus influenza	Haemophilus influenzae
Prostatitis	Staphylococcus	Staphylococcus

Oral Pain Furuncul fever Pyelitis	Streptococcus	...	Streptococcus	...
	Gonococcus	...	Neisseria gonorrhoeae	...
	Diphtheroids	...	Corynebacterium hofmannii	...
	Bacterium psittacosis	...	Salmonella psittacosis	...
	Streptococcus	...	Streptococcus haemolyticus	...
Rat-bite fever Relapsing fever	Colon bacillus	...	Escherichia coli (Bact. coli)	...
	Bacillus coli communior	...	Escherichia communior (Bact. communior)	...
	Bacillus proteus	...	Proteus vulgaris	...
	Streptococcus faecalis	...	Streptococcus faecalis	...
	Bacillus pyocyaneus	...	Pseudomonas aeruginosa (Pa. pyocyanea)	...
Rhinitis	Gonococcus	...	Neisseria gonorrhoeae	...
	Bacillus aerogenes capsulatus (rarely)	...	Clostridium welchii	...
	Spirochaeta morsus muris	...	Spirillum minus	...
	Spirillum of relapsing fever	...	Borrelia recurrentis	...
	Spirochaeta duttoni	...	Borrelia duttoni	...
Rheumatic fever	Spirochaeta novyi	...	Borrelia novyi	...
	Spirochaeta carteri	...	Borrelia carteri	...
	Staphylococcus pyogenes aureus	...	Staphylococcus aureus	...
	Streptococcus erysipelatis	...	Streptococcus erysipelatis	...
	a streptococcus	...	Streptococcus viridans	...
Rhinoscleroma Scarlet fever Sinusitis	Diplococcus siccus	...	Neisseria pharyngis sicca	...
	Bacillus segirentosus	...	Corynebacterium segmentosum	...
	Bacterium fastidium	...	So'monella fastida	...
	Diphtheria bacillus	...	Corynebacterium diphtheriae	...
	Streptococcus	...	Streptococcus (rheumaticus)	...
Synovitis	Virus (unidentified)	...	Klebsiella rhinoscleromatis	...
	Bacillus of rhinoscleroma	...	Streptococcus scarlatinae	...
	Streptococcus scarlatinae	...	Staphylococcus	...
	Staphylococcus	...	Diplococcus pneumoniae (Strepto. pneumo- niae)	...
	Pneumococcus	...	Streptococcus pyogenes	...
Synovitis	Streptococcus pyogenes	...	Haemophilus influenzae	...
	Influenza bacillus	...	Neisseria gonorrhoeae	...
	Gonococcus	...	Mycobacterium tuberculosis	...
Synovitis	Tubercle bacillus
	
	

PATHOGENIC BACTERIA

Disease	Common Name	Modern Nomenclature
Syphilis	Bacillus typhosus	Eberthella typhi (Bact. typhosum)
Tetanus	Pneumococcus	Diplococcus pneumoniae (Streptococcus pneumoniae)
Leptospirosis	Spirochaeta pallida	Treponema pallidum
	Tetanus bacillus or Bacillus of lockjaw	Clostridium tetani
	White staphylococcus	Staphylococcus albus
	Streptococcus pyogenes	Streptococcus pyogenes
	Pneumococcus	Diplococcus pneumoniae (Strepto. pneumoniae)
Tuberculosis (human)	Tubercle bacillus	Mycobacterium tuberculosis (hominis)
Tuberculosis (bovine)	Bovine tubercle bacillus	Mycobacterium tuberculosis (bovis)
Typhoid fever	Bacterium tularensis	Pasteurella tularensis
Typhoid fever	Typhoid bacillus or Bacillus typhosus	Eberthella typhi (Bact. typhosum)
Urethritis	Gonococcus	Neisseria gonorrhoeae
	Colon bacillus	Escherichia coli (Bact. coli)
	Streptococcus	Streptococcus
	Staphylococcus	Staphylococcus
	Gonococcus	Neisseria gonorrhoeae
	Staphylococcus	Staphylococcus
	Streptococcus	Streptococcus
	Bacillus coli communior	Escherichia communior (Bact. communior)
	Staphylococcus	Staphylococcus
	Bacillus putrificus	Clostridium putrificum
	Vibrio septique	Clostridium oedematis maligni (Clostridium septique)
	Bacillus oedematis	Clostridium oedematis
	(Gas-oedema bacillus)	Clostridium novyi
	Bacillus oedematis	Clostridium welchii
	Bacillus welchii (Bacillus aerogenes cap- sulated)	Corynebacterium xerosis
	Bacillus xerosis	Treponema pertenue
Xerosis	Spirochaeta pertenuis	
Yaws		

Summary of Life History and Distribution of Intestinal Nematodes Found in Man

Name of parasite and geographical distribution	Site of adult	Larvæ	REMARKS
<i>Ascaris lumbricoides</i> Cosmopolitan <i>Enterobius vermicularis</i> Cosmopolitan	Intestine of man Mature males and females in small intestine of man. Gravid females in rectum	Developed within the egg and are swallowed by man Developed within the egg and are swallowed by man	• Male dies after fertilizing female in small intestine
<i>Strongyloides stercoralis</i> Tropical and subtropical; very unequal	Lungs and mucosa of jejunum of man	Rhabditiform larvæ passed in feces may (a) develop into infective filariform larvæ, or (b) develop into free-living males and females which produce numbers of rhabditiform larvæ; these develop into infective filariform larvæ	Larvæ penetrate unbroken skin
<i>Trichinella spiralis</i> Cosmopolitan, but rare	Small intestine of man, also found in pig; usually a parasite of rats	Each gravid female deposits larvæ over a period of three weeks in the blood stream, these encyst in striated muscle and are infective to another host when eaten	Viviparous
<i>Trichuris trichiura</i> Cosmopolitan	Cæcum of man	Developed within the egg and are swallowed by man	—
<i>Ancylostoma duodenale</i> <i>Necator americanus</i> Tropical and subtropical; very unequal, and locally in temperate zones	Small intestine of man	Developed within the egg; escape and become infective in soil	Larvæ penetrate unbroken skin

(Parasitology, Blacklock and Southwell)

Summary of Life History and Distribution of the Filarioidea Found in Man

Name of parasite and geographical distribution	Site of adult	Larvæ	Host of larvæ
<i>Wuchereria bancrofti</i> Tropical and sub-tropical unequal	In lymph glands and spaces	In peripheral blood ; nocturnal ; sheathed	Various species of mosquitoes
<i>Loa loa</i> West Africa	Worms in connective tissue ; migratory	In peripheral blood ; diurnal ; sheathed	<i>Chrysops</i> spp.
<i>Diastelomena perstans</i> Africa and South America	In mesentery	In peripheral blood ; non-periodic ; unsheathed	<i>Culicoides</i> spp.
<i>Filaria</i> 'ozzardi' West Indies	In mesentery	In peripheral blood ; non-periodic ; unsheathed	Unknown
<i>Onchocerca volvulus</i> Africa ; Central and South America	In subcutaneous tumours usually	In subcutaneous tumours and skin ; non periodic ; unsheathed	<i>Simulium</i> spp.
<i>Agamofilaria</i> 'streptocerca' West Africa	Adult unknown	In cutaneous tissue, non-periodic ; unsheathed	Unknown
<i>Dracunculus medinensis</i> Tropical America, Nile valley, Arabia, Persia, Turkestan, India, Ceylon, Fiji, Africa, and West Indies	Gravid female causes superficial ulcers on skin in frequent contact with water	In ulcers on the skin ; non-periodic ; unsheathed	<i>Cyclops</i>

(Parasitology, Blacklock and Southwell)

Pathogenic Protozoal Parasites of Man

Class	Species of parasite	Disease caused	Geographical distribution
Rhizopoda	<i>Endamoeba histolytica</i>	Amoebiasis Amoebic dysentery	Tropics, sub-tropics and temperate zones
Mastigophora	1. <i>Trypanosoma gambiense</i>	Trypanosomiasis	Africa
	2. <i>Trypanosoma cruzi</i>	Trypanosomiasis	S. America
	3. <i>Leishmania</i> spp.	Leishmaniasis (a) Kala-azar (b) Infantile kala-azar (c) Tropical sore (d) Espundia	Assam, India Mediterranean Persia S. America
Sporozoa	1. <i>Plasmodium falciparum</i>	Malaria	Tropics, sub-tropics and temperate zones
	2. <i>Plasmodium vivax</i>		
	3. <i>Plasmodium malariae</i>		
	4. <i>Plasmodium ovale</i>		
Ciliata	<i>Balantidium coli</i>	Balantidial dysentery	Tropics, sub-tropics and temperate zones

(Parantology, Blacklock and Southwell)

Stages of Parasites Infective for Man and Where Found

Name of parasite	Infective stage for man and where found	Mode of infection
<i>E. histolytica</i>	Cysts in faeces of man	A, f and u
<i>T. granbiense</i>	Metacyclic trypanosomes in salivary glands of tse tse	I.
<i>T. cruzi</i>	Metacyclic trypanosomes in faeces of reduviid bugs	C.
<i>L. donovani</i>	(?) Metacyclic forms in bed-bugs and sandflies	(?)
<i>P. falciparum</i> M. T. }	Sporozoites () in salivary glands of anopheline mosquitoes	I.
<i>P. vivax</i> S. T. }		
<i>P. malariae</i> Q. }		
<i>P. ovale</i>		
<i>B. coli</i>	Cysts in faeces of pig and man	A, f and u.
<i>S. pallida</i>	Spirochaetes in primary and secondary lesions	S. (?) I.
<i>S. recurrentis</i>	Spirochaetes in haemocoel of lice and ticks	A, f and u.
<i>S. teterohæmorrhagæ</i>	Spirochaetes in urine of infected rats : in water	S.
<i>Sp. minus</i>	Spirilla in mouth of infected rats	A, (M).
<i>T. solium</i>	Cysticercus cellulosa in pork	A, f and u.
<i>C. cellulosa</i> in man	Eggs in faeces of man	A, (M).
<i>T. Ægnota</i>	Cysticercus bovis in beef	A, f and w.
<i>H. nana</i>	Eggs in faeces of rat and man	A, (V).
<i>D. latus</i>	Plerocercoid in fresh-water fish	(?) A, u.
<i>Dibothriocephalus</i> sp. (sparganosis)	(?) Plerocercoid in (?) <i>Cyclops</i>	A, f and u.
<i>T. granulosa</i> larva ; hydatid cyst	Eggs in faeces of dog, fox and cat	S and A.
<i>S. hæmatobium</i> }	Cercaria in water, free swimming	A (M).
<i>S. mansoni</i> }		
<i>S. japonicum</i> }	Cercaria in fresh-water fish	A, (M).
<i>C. sinensis</i> }		
<i>H. heterophyes</i> }	Cercaria in fresh-water crabs and crayfish	A, (M).
<i>P. westermani</i> }		

<i>P. hepaticæ</i>	...	Cercaria on blades of grass, encysted	...	A, f and w.
<i>F. buskii</i>	...	Cercaria on fresh-water plants, encysted	...	A, f and w.
<i>A. lumbricoides</i>	...	Eggs containing larvæ in soil and water contaminated with feces of man	...	A, f and w.
<i>E. vermicularis</i>	...	Eggs containing larvæ on skin around the anus	...	A, f and w.
<i>T. spiralis</i>	...	Encysted larvæ in muscle of pork	...	A, (M).
<i>T. trichiura</i>	...	Eggs containing larvæ in soil and water	...	A, f and w.
<i>S. stercoralis</i>	...			
<i>A. duodenale</i>	...			
<i>N. americanus</i>	...	Filariform larvæ in soil, in latrines and water	...	S, A, f and w.
<i>W. bancrofti</i>	...			
<i>L. loa</i>	...	Mosquitoes; full-grown larva in mouth parts	...	S.
<i>D. persians</i>	...	<i>Chrysops</i> ; full-grown larva in mouth parts	...	S.
<i>F. ozzardi</i>	...	<i>Culicoides</i> ; full-grown larva in mouth parts	...	S.
<i>O. volutus</i>	...	<i>Culicoides</i> ; full-grown larva in mouth parts	...	S.
<i>A. streptocæca</i>	...	<i>Simulium</i> ; full-grown larva in mouth parts	...	(?) S.
<i>D. medinensis</i>	...	(?) Larva in mouth parts of some insect	...	A, w.
	...	<i>Cyclops</i> ; full-grown larva in body	...	

A=Infection of man by way of the alimentary canal, i.e., ingestion of contaminated water or food, especially raw vegetables.

f=In food.

S=Infection of man by the skin or mucous membrane, the larva, or the virus penetrating directly or through lesions.

I=Inoculative method by insect vector.

C=Contaminative method by insect or tick vector.

w=In water.

(M)=meat, fish or edible crustacea.

(Parasitology, Blacklock and Southwell)

Arthropod Vectors of Diseases in India

Malaria-carriers (Anopheline). Out of 42 species with 10 varieties 7 are proved carriers.

(A) Proved malaria-transmitting species.

1. *Anopheles culicifacies*. Punjab South-west, Rajputana East, Sind, United Provinces East, United Provinces West, Waziristan, Assam, Baluchistan, Bengal, Berar, Bihar, Bombay Deccan, Burma (Lower and Upper), Central India (East and West), Central Provinces (East and West), Ceylon, Chotanagpur, Delhi Provinces, Gujrat, Hyderabad (North and South), Kashmir, Konkan, Madras Coast North, Madras Deccan, Madras South East, Malabar, Mysore State, Nepal, N. W. F. P., Orissa, Punjab (East and North).

2. *A. minimus*. Assam, Bengal, Bihar, Burma, (Upper and Lower), Chotanagpur, Konkan, Madras Coast (North), Madras (Deccan), Madras (South-east), Malabar, Mysore State, United Provinces West.

3. *A. fluviatilis (listoni)*. Assam, Baluchistan, Bengal, Berar, Bihar, Bombay Deccan, Burma Lower, Burma Upper, Central India East, Central India West, Central Provinces West, Ceylon, Chotanagpur, Delhi Province, Gujrat, Hyderabad North, Kashmir, Konkan, Madras Coast North, Madras, Deccan, Madras South East, Malabar, Mysore State, Nepal, N. W. F. P., Orissa, Punjab (East and North), Punjab (South-west), United Provinces (East and West), Waziristan.

4. *A. philippinensis*. Andamans, Assam, Bengal, Bihar, Burma (Upper and Lower), Chotanagpur, Konkan, Malabar, Mysore.

5. *A. stephensi*. Assam, Baluchistan, Bengal, Berar, Bihar, Bombay (Deccan), Burma (Lower and Upper), Central India (West), Central India (East), Central Provinces (East and West), Chotanagpur, Delhi Provinces, Gujrat, Hyderabad (North and South), Kashmir, Konkan, Madras Coast (North), Madras Deccan, Madras South-east, Malabar, Mysore State, N. W. F. P., Punjab (East and North), Punjab (South-west), Rajputana East, Sind, United Provinces (East and West), Waziristan.

6. *A. sundaeus (ludlowii)*. Bengal, Burma Lower.

7. *A. varuna*. Bengal, Burma Upper, Ceylon, Chotanagpur, Konkan, Madras Coast North, Madras South-east, Malabar, Orissa, United Provinces (East).

(B) Species found infected in nature in Indian areas.

A. annularis (fuliginosus), Assam, Bengal, Berar, Bihar, Bombay, Deccan, Burma Lower, Burma Upper, Central India (East and West), Central Provinces (East and West), Ceylon, Chotanagpur, Delhi Province, Gujrat, Hyderabad South, Kashmir, Konkan, Madras Coast North, Madras Deccan, Madras (South-east), Malabar, Mysore State, Nepal, N. W. F. P., Orissa, Punjab (East and North), Punjab (South-west), Rajputana East, Sind, United Provinces (East and West), Waziristan.

A. maculatus, *A. maculatus* var. *willmori*, *A. pulcherrimus*, *A. maculipalpis*, *A. pallidus*, *A. ramsayi*, *A. vagus*.

(C) Species that are important carriers in other countries but of too limited distribution to be important in India.

A. superpictus, *A. multicolor*.

Yellow fever carriers (Culexini). Five prospective carriers.

(A) Proved carrier.

Aedes (Stegomyia) aegypti. Cosmopolitan (more or less).

(B) Suspected carriers.

Aedes (stegomyia) vittatus. Widely spread from the North-west Frontier to Assam and Burma and through Peninsular India to Ceylon. At Pusa (N. Bihar), it occurs throughout the year, but is commonest in the rains.

Aedes (stegomyia) albopictus. A very common species throughout India, including Assam and Burma, also in the Andamans and Ceylon, occurs up to 5,000 to 6,000 ft. in the hills.

Aedes (stegomyia) scutellaris. In Indian region, Andamans.

Mansonia (mansonioides) uniformis. Common in most parts of India (including Assam, Burma, Peninsular India) and Ceylon; less common in the North-west, but specimens have been received from the United Provinces, Punjab, Sind and Bombay. Often abundant and a troublesome blood-sucker.

Dengue carrier

Aedes (stegomyia) aegypti.

Filaria (Wuchereria) bancrofti carriers**(A) Proved carrier.**

Culex (culex) fatigans. One of the most abundant of Indian culicini. Found in all parts of the Indian region, and is largely a domestic mosquito. It occurs up to 5,000 ft. or more in the hills. In parts of the country it is most probably concerned in the transmission of filariasis.

(B) Suspected carriers (species infected under laboratory conditions).

Anopheles hyrcanus var. *nigerrimus*, *A. barbitrostris*, *A. subpictus*, *A. sundanicus* (Iudlowii), *A. stephensi*, *A. fuliginosus*, *A. pseudojamesti*, *A. varuna*, *A. pallidus*, *A. philippinensis*, *Culex vishnui*.

Microfilaria malayi carrier

Mansonia (mansonioides) annulifera. Bihar and Orissa, Bengal, Assam, Burma, East and South-west coast of Indian Peninsula and Ceylon, Fyzabad (U. P.) and Central Provinces, does not appear to occur west of a line drawn from the western boundary of Nepal to Bombay.

Papatacci fever carrier

Phlebotomus papatasi. Very widely distributed over the northern and western regions of India, and on the plains of the Punjab and N. W. F. P. the sandflies consist almost entirely of this species and *P. minutus*. It does not appear to be found east of Pusa in Bihar and Orissa or south of Poona in the Bombay Presidency. Although it is essentially a plain living species and appears to be absent from the Himalayas at heights over 2,000 ft. Yet it has been reported in the hotter and comparatively drier valleys of the Hindukush Mountains at heights of 4,500 ft. and at Quetta, Baluchistan (about 5,500 ft.) in which places the climates more nearly approximate that of the plains than the moister and cooler slopes of the Himalayas.

Its seasonal prevalence is that described for the 'sandflies' of the Punjab and N. W. F. P. Its period of maximum prevalence more or less coincides with that of 'papatacci fever.' It also occurs in environs Calcutta.

Leishmania donovani carrier (?) (Kala-azar)

Phlebotomus argentipes. Occurs commonly all along the east coast of India, from Bengal to Ceylon, from sea level up to 1,500 ft. Like Kala-azar its distribution seems to be bounded on the north and west by a line joining Bombay and Delhi. Successful transmission experiments have been carried out with animals by the bite of *P. argentipes*.

Leishmania tropica carrier (?) (Oriental sore)

Phlebotomus sergenti. Seems to occur under somewhat similar conditions of climate and altitude to those which are favourable to *P. papatasi* but is a much rarer species. Its distribution seems to be extraordinarily localised in the areas in which it occurs. Like Oriental sore it seems only to occur in the parts of India north and west of the line joining Bombay and Delhi. (1) The Punjab strain of *L. tropica* develops in *P. sergenti* in a manner indicating a definite host parasite relationship. (2) The flagellate forms of *L. tropica* which develop in *P. sergenti* are infective when inoculated intradermally into a susceptible animal. (3) The flagellate infection is infective as early as the 5th day after the initial feed of the fly.

House flies (Muscidae)

Probable carriers of *Bact. typhosum* and allied species, cholera vibrio and allied species, bacteria of summer diarrhoea, bacteria affecting eye, pathogenic protozoa.

Musca domestica. Cosmopolitan.

Musca corvina. Widely distributed.

Musca determinata. Widely distributed.

Other members of genus *Musca*. *M. vicina*, *M. nebula*, *M. sorbens*. Blue and Green bottles are also probable carriers.

Genus. *Pycnosoma*, *Thelychata* and *Pyrellia*.

Well-known species are *Calliphora erythrocephala* (hills); *Lucilia suprina* (serenissima); Green bottle—*Chrysomya megacephala* and *Chrysomya bezziana*.

Myiasis producing (Muscidae)

Pycnosoma flaviceps. Nostrils of human beings and camels.

Chrysomya bezziana Myiasis of carious tooth.

Sarcophaga fuscicauda, *Aphiochæta scalaris* and *Sarcophaga hirtipes* and accidental myiasis carriers.

Blood sucking (Muscidae)

Important from veterinary point of view only.

Genus. *Stomoxys*, *Hæmatobia*, *Bdellolarynx*, *Lyperosia*, *Philæmatomyia*. These with some species of *Tabanidae* carry the parasite which causes 'Surra' or Trypanosomiasis of cattle.

Plague carriers

Bacillus pestis carriers (Siphonaptera). Schedule of species of rat flea found in regions liable to plague infection.

PUNJAB. *Xenopsylla cheopis*, *X. astia*, *Ceratophyllus punjabensis*.

BOMBAY. *X. cheopis*, *X. braziliensis*, *X. astia*.

UNITED PROVINCES. *X. cheopis*, *X. astia*.

CENTRAL INDIA. *X. cheopis*, *X. braziliensis*, *X. astia*.

MADRAS. *X. cheopis*, *X. astia*, *X. braziliensis*, *C. nilgiriensis*, *Leptopsylla musculli*.

Asiatic Relapsing fever-carriers (Lice)

Pediculus humanus corporis (body louse) is the natural transmitter of spirochæte of relapsing fever to man.

Pediculus humanus capitis (head louse) also transmits the disease.

Tick-Typhus carriers (?) (Acarina).

List of species of Ticks collected from Tick-Typhus areas.

Boophilus australis. Chin Hills, Shillong, Muktesar (Nainital Dist.), Burma, Bengal, Bihar and Orissa, Central Provinces, Madras Presidency, South Bombay, Hazara Dist. (N. W. F. P.), Dalhousie (Gurdaspur Dist.), Dharampur and Kasauli (Simla Hills).

Hyalomma aegyptum. Punjab, Sindh, Rajputana, United Provinces, Bihar and Orissa, Central Provinces, Madras and Bombay Presidencies. Rare in Bengal and Ceylon, Seistan and Perso-Baluchistan Frontier.

H. aegyptum. sub sp. *isaaci* Sheriff. Nepal, Bihar and Orissa, United and Central Provinces, Punjab, Madras and Bombay Presidencies.

H. (hyalomina) hussaini Sheriff. Bihar and Orissa, Central Provinces, Madras and Bombay Presidencies.

H. (hyalomina) hussaini, var. *brevipunctata*. Bengal, Bihar and Orissa, Central Provinces, Madras and Bombay Presidencies.

Rhipicephalus sanguineus. India, Burma, Ceylon. Cosmopolitan.

Hæmaphysalis bispinosa. Upper Burma, Lower Burma, Assam, Bengal, Bihar and Orissa, Central Provinces, Madras and Bombay Presidencies, Punjab, Andamans.

Miscellaneous maladies caused by insects and other Arthropods

VESICULAR DERMATITIS. *Lytta tenuicollis* (Coleoptera).

'SPIDER (?) LICK.' *Pedderus fuscipes* (Staphylinids).

'NAGA SORE' AND EPIDEMIC CONJUNCTIVITIS. *Siphonella funicola* (Osciuidæ).

INTESTINAL 'SCARABIASIS.' *Onthophagus bifasciatus*, *Caccobius mutens* (Coleoptera).

IRRITATION, DERMATITIS AND PIGMENTATION OF THE SKIN. *Pediculus humanus corporis* (Body louse).

IRRITATION. *Pediculus humanus capitis* (Head louse), *Phthirus pubis* (Pubic louse).

ITCH. *Sarcoptes scabiei* (Itch mite).

Guinea worm carriers (?) (Crustacea)

'Guinea worm' (*Dracunculus medenensis*). *Cyclops coronatus*, *C. bicuspidatus*, *C. quadricornis*.

Indian Scorpions

Distribution of Genera and Species

1. **BUTHEOLUS** Simon. Eastern Mediterranean area of Palearctic Region; shores of Red Sea; Sokotra; Western and North-Western India.

B. bicolor Pocock. Western Ghats: Khandala, Wai, Satara, Poona.

B. flavescens Pocock. Kathiawar: Kharagoda.

**B. melanurus* Kessler. Northern Baluchistan; Waziristan: Sewa; Punjab; Ahmednagar: Shevgaon.

B. pallidus Pocock. Sind: Kashmor Bund, Khelat Frontier.

2. **BUTHUS** Leach. Mediterranean area of Palearctic Region; Siopia Region down to Zambesi; China; India, but absent from Ceylon, Burma.

B. acute-carinatus Simon. Sind: Hyderabad; Waziristan: Miran-shah; Central India: Gwalior.

B. alticola Pocock. Chitral; North-West Frontier: Malakand, Peshawar; Punjab.

B. atrostriatus Pocock. Sind: Kashmir Bund.

B. australis Linn. Northern Baluchistan; Sind: Hyderabad, Kotri, Kashmir Bund, Khelat Frontier, Punjab: Maurypur, Laharpur

B. caucasicus Fischer. Northern Baluchistan.

B. doriae Thorell. Sind: Karachi, Khelat Frontier; Baluchistan: Ormara on the Mekran coast.

B. hendersoni Pocock. Bilaspur: Nandghat; Raipur: Drug; Cud-dapah; North Arcot, Chingleput: Madras; Salem: Yercaud in the She-varoy Hills; Trichinopoly; Tanjore.

B. macmahoni Pocock. Northern Baluchistan.

B. nigrifrons Pocock. Northern Baluchistan.

B. pachyurus Pocock. Mandla; Nagpur: Nagpur, Kamptee; Nasik; Satara; Godavari: Tanuku.

B. rugiscutis Pocock. Western Ghats: Satara, Mahabaleshwar, Paichgani.

B. tamulus Fabr. Waziristan: Miran-shah, Banks of Chasma River; Dehra Dun; Garhwal: Srinagar; Bareilly; Shikarpur: Khelat Frontier; Karachi: Jati, Kotri Sujawal; Hyderabad, Aligarh: Jalali; Shahjahan-pur: Katra; Sitapur: Laharpur; Gwalior; Jhansi; Moth; Banda: Bharatkup; Benares, Allahabad: Munjhanpur; Ghazipur; Shahabad: Sarinja; Patna; Gaya: Arwal: Santal Parganas: Amrapara; Mahi-Kantha: Ilol; Kathiawar: Kharagoda; Panch Mahals; West Khandesh: Sakri; Bhopal; Saugor, Jubbulpur: Satna, Narsinghpur; Bilaspur: Bilas-pur, Lormi; Calcutta; Puri: Kakatpur; Raipur: Drug; Balaghat; Nag-pur; Chanda: Ahiri, Allapilli, Sironcha; Yeotmal: Dhanoba; Akola: Boriadgaon; Amraoti, Nimar: Khandwa, Buldana; Nasik: Dindori, Niphad; Thana: Shahapur; Ahmednagar: Shevgaon; Bombay: Salsette, Poona: Khandala; Ratnagiri; Satara; Kolhapur; Belgaum: Gokak; Bija-pur: Badami, Bagalkot, Bagewadi, Bijapur, Bilgi, Guledgudd, Muddebihal, Talikoti; Secunderabad; Vizagapatam: Anakapalle, Chodavaram Nakkapalli; Godavari: Dowlaishwaram, Kothapet, Tanuku, Yeleshwaram; Kistna: Nuzvid; Guntur: Addanki, Kollur; Nellore; Kurnool; Ananta-pur: Uravakonda; Bellary: Kanakal; Dharwar; North Kanara: Karwar; Chitaldroog; Holalkere; Tumkur: Chiknayakanhalli, Pavagada; Kolar: Hosur, Sidlaghatta; North Arcot, Arni, Chetpat, Polur; Chingleput: Madras; Bangalore: Bangalore, Closepet, Chikkabanavara, Yelahanka; Mysore: Attikan, Mysore, Nagamangala; Hassan: Saklasnur, Shukra-vankot; South Kanara: Katapadi; Coimbatore: Bhavani; Trichinopoly: Karur, Trichinopoly; Tanjore: Swamimalai, Tanjore, Tirupanandal; Madura.

3. *CHARMUS* Karsch. Ceylon.

4. *lanens* Karsch. Ceylon.

C. *HEMIRUTHUS* Pocock. India.

H. *crassimanus* Pocock. Western India: Panch Mahals.

5. *ISOMETRUS* Hempr. and Ehrenb. Oriental Region, from India as far east as Queensland.

I. *acanthurus* Pocock. Kolaba: Matheran.

I. *assamensis* Oates. Assam: Dhubri; Puri: Kakatpur.

I. *basiliens* Karsch. Ceylon: Haldumullah, Peradeniya.

I. *chryseus* Pocock. South Kanara: Mangalore.

I. *orientalis* Linn. Karachi; Bombay; Thana: Salsetta; Ceylon: Peradeniya, Trincomalee; Burma: Akyab, Rangoon; Andaman Islands.

- I. rigidulus* Pocock. Central India: Bhopal.
I. thurstoni Pocock. Bhopal; Kolhapur; Belgaum; Cuddapah; Salem: Yercaud in the Shevaroy Hills; Nilgiris: Coonoor; Malabar: Manjeri; Trichinopoly; Tinnevely.
I. thwaitesi Pocock. Ceylon.
I. vittatus Pocock. Madras.
6. **LYCHAS** C. Koch. Tropical Africa; India to Australia.
L. fene Thorell. Burma: Shwegoo.
L. hendersoni Pocock. Salem: Yercaud in the Shevaroy Hills.
L. laevifrons Pocock. Calcutta.
L. mucronatus Fabr. Upper and Lower Burma; Tenasserim.
L. nigristernis Pocock. Dehra Dun.
L. rugosus Pocock. Central Provinces: Raipur
L. scaber Pocock. Secunderabad; Madras.
L. scutillus C. Koch. Southern Tenasserim.
L. shoplandi Oates. Lower Burma: Prome; Pegu: Entagaw; Palone, Rangoon.
L. tricarinatus Simon. Bhopal; Nagpur; Kamptee; Belgaum; North Kanara; South Kanara; Mangalore; Nilgiris; Travancore: Trivandrum; Tanjore; Salem: Yercaud in the Shevaroy Hills, South Arcot; Pondicherry; Chingleput; Madras; Nellore.
7. **PLESIOBUTHUS** Pocock. India.
P. paradoxus Pocock. Northern Baluchistan.
8. **STENOCHIRUS** Karsch. Malabar Coast, hills of Ceylon.
S. politus Pocock. Kanara.
S. sarasinorum Karsch. Ceylon: Peradeniya.
9. **CHÆRILUS** Simon. Ceylon; Himalayas from Kashmir to Assam; Burma, Malacca, Sumatra, Java, Borneo and Celebes.
C. ceylonensis Pocock. Ceylon: Trinomalee.
C. gemmifer Pocock. Sylhet.
C. granosus Pocock. Western Himalayas: Mussoree.
C. insignis Pocock. Ladakh.
C. margaritatus Pocock. Simla Hills: Kasauli.
C. pictus Pocock. Sylhet.
C. tricostratus Pocock. Assam: Sadiya.
10. **CHIROMACHETES** Pocock. Malabar Coast in Southern India.
C. fergusonii Pocock. Travancore: Trivandrum.
11. **HEMISCORPIUS** Peters. Sokotra, Baghdad and Baluchistan.
H. lepturus Peters. Northern Baluchistan.
12. **HORMURUS** Thorell, India; Burma; the whole of the Indo- and Austro-Malayan area; Polynesia and Melanesia.
H. australasiae Fabr. Burma—Akyab; Prome; Toungoo; Thagaya; Henzada; Myanaung; Pegu Hills; Amherst: Kawkareik, Moulmein; Tavoy; Mount Mooleyit in Tenasserim; Reef Island; Great Cocos Island; Andamans; Nicobar Islands.
H. nigripes Pocock. Panch Mahals; Jubbulpore: Satna.
13. **IOMACHUS** Pocock. British and German East Africa; S. India.
I. laeviceps Pocock. South Kanara: Mangalore; Nilgiris: Kotagiri; Salem: Yercaud in the Shevaroy Hills.
I. nitidus Pocock. Nellore.
I. punctulatus Pocock. Nilgiri Hills; Coimbatore

14. *PALAMNÆUS* Thorell. Oriental Region from Indian and Ceylon to Borneo and the Philippines.

P. barberi Pocock. Tinnevely.

P. bengalensis C. Koch. Dehra Dun: Sahaspur; Gwalior; Allahabad, Benares; Jubbulpore: Satna; Chota Nagpur; Bengal; Assam-Sibsagar.

P. cæsar C. Koch. Ceylon.

P. fulvipes C. Koch. Ajmere; Banda: Bharatkup; Mähi-Kantha: Himatnagar, Ilol; Kathiawar: Kharagoda; Panch Mahals; Narsinghpur; Bhandara: Nawegaon; East Satpura Hills; East Khandesh: Chalisgaon, Talegaon; West Khandesh; Nasik: Chandor, Kalvan, Malegaon, Nandgaon, Niphad, Yeola; Belgaum: Saundatti; Bijapur: Badami, Bagalkot, Bijapur, Bilgi, Guledgudd; Secunderabad; Kistna: Nuzvid, Cuddapah, Tamkur. Chiknayakanhalli; North Arcot: Chetput, Polur; Chingleput: Madras; Bangalore: Chikka-banavara; Mysore: Bilikere, Krishnaja-sagara, Nagamangala; Travancore: Ellappatti.

P. gravimanus Pocock. Mysore: Attikan; Tanjore; Ceylon.

P. indus De Geer. Ceylon: Peradeniya.

P. latimanus Pocock. ?

P. lirus Pocock. Gwalior; Narsinghpur; Bhopal.

P. longimanus Herbst. Burma: Cinchona Plantation; Thaton: Mokpalani Quarries; Andamans: Port Blair.

P. oatesii Pocock. Hanthawaddy: Rangoon; Mergui.

P. phipsoni Pocock. Aligarh: Jalali; Nasik Ghats; Nasik: Dindori, Lena, Peint; Thana; Bombay; Kolaba: Matheran; Poona: Khandala, Kolhapur: Bhudhargarh, Panhala; Bijapur: Badami; Godavari: Tanuku, Mysore; Adikkan; Nilgiri Hills; Coimbatore: Billigirirangan Hills at 4,000 to 5,000 feet; Salem: Yercaud in the Shevaroy Hills.

P. scaber Thorell. Dharwar; North Kanara; South Kanara, Coorg; Malabar; Travancore: Trivandrum.

P. serratus Pocock. Ceylon.

P. swammerdami Simon. Dehra Dun; Saran: Siwan; Shahabad, Burdwan; Chota Nagpur; Sambalpur; Jubbulpore, Satna; Narsinghpur, Raipur; Nimar: Khandwa; Bijapur: Talikoti; Belgaum: Saundatti; Dharwar; Vizagapatam: Chodavaram, Godavari: Chintur, Dowlishwaram, Tanuku, Yelleshwaram; Kistna: Nuzvid; Anantapur: Hindupur; Shimoga: Davangere; North Arcot: Polur; Chingleput: Madras; Bangalore: Yelahanka; Mysore: Bilikere, Krishnajasagara, Mysore, Nagamangala, Periyapatna; Nilgiris: Coonoor; Coimbatore: Bhavani; Trichinopoly; Tanjore; Ramnad; Ceylon: Chilan, Trincomalee.

P. wroughtoni Pocock. Kolhapur: Gadingal; Belgaum.

P. xanthopus Pocock. Bilaspur: Lormi; Chanda: Ahiri; Satara; Bijapur: Badami; Mysore: Bilikere.

15. *SCORPIOPS* Pters. The Deccan; Himalayas from the Punjab to Assam, thence through Burma to Southern Tenasserim.

S. anthracinus Simon. Tavoy.

S. asthenurus Pocock. Darjeeling: Kalimpong; Cachar: Haflong.

S. binghami Pocock. Pegu Hills; Central Tenasserim.

S. crassimanus Pocock. —?

S. hardwickii Gervais. Himalayas; Kashmir; Jaunsar 6,000 to 9,000 feet; Dehra Dun 2,000 feet; Kasauli; Nepal.

S. insculptus Pocock. Jaunsar 6,000 to 9,000 feet; Dehra Dun 2,000 feet.

Leptochirus Pocock. Assam; Sadiya; Garo Hills: Tura.

S. lindstræmii Thorell. North Chin Hills; Mount Mooleyit in Tenasserim.

S. longimanus Pocock. Assam: Sylhet, Dhubri, Sadiya; North Cachar Hills; Naga Hills.

S. montanus Karsch. Waziristan: Razmak, Mount Shuidar 8,000 feet; Kangra: Dharmasala; Jaunsar 6,000 to 9,000 feet; Simla: Kasauli; Dehra Dun 2,000 feet; Garhwal: Srinagar; Moradabad; Sitapur; Laharpur, Misrih; Kolaba: Matheran; Satara: Mahabaleshwar.

S. petersii Pocock. Jaunsar 6,000 to 9,000 feet; Simla; Dehra Dun 2,000 feet, Mussorée.

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Distribution of Poisonous Snakes in the World

Serpents have great ability of adopting themselves to low temperatures and select favourable hibernating places during very cold weather. Practically in all parts of the world where reptile life is possible snakes will be found. In the northern hemisphere they are found as high as 50° latitude in Canada, and the European viper is found in Siberia. The United States is rich in serpent life and a great number of them are poisonous. In Europe snakes are scanty there being only about a dozen non-venomous and half a dozen venomous types. The latter are *Vipera berus*, *V. aspis*, *V. latastii*, *V. ammodytes*, and *V. orsini*.

The Viper is never found in Ireland although it is common in England and Scotland. Hawaii has no poisonous snakes. The poisonous snakes in Europe are of small size and their bites only cause local symptoms and are rarely fatal to man. The adder is the only poisonous snake found in Great Britain. It ranges from Wales to the Saghalien Island and from Caithness to the north of Spain, and has been met with at an elevation of 9,000 ft. It occurs also in the northern parts of Scandinavia and is the only venomous snake found beyond the Arctic Circle. The Asp is found all over southern Europe, and in large numbers in the Alpine regions.

Of the 10 varieties of cobras in the world (1) *Naja naja*, (2) *N. bungarus*, (3) *Hemii bungarus*, (4) *Boulengerina*, (5) *Elapichis*, (6) *Sepedon*, (7) *Aspidelaps*, (8) *Walterinnesia*, (9) *Hamorelaps*, (10) *Dendrasphis*, the last eight are found outside India. Varieties 1, 4, 5, 6, 8, 9, 10 occur in Africa, the most widely distributed being the Egyptian cobra and the Black-necked cobra. The Cape cobra (*N. flava*) is found in the Cape Province of South Africa. A particularly interesting variety is the Ringhal, or Spitting snake (*Spedon hamachates*) of South Africa which occurs nowhere else in the world. The most dreaded snake in Tropical and South Africa is the Mamba or Tree cobra. It occurs in two varieties: black and green (*Dendraspis angusticeps* and *D. viridis*). The green mamba grows to a length of 9 feet, and the black one to as much as 13 feet. The black mamba, which is the more fierce and aggressive of the two, is the largest venomous snake in Africa and next to

the King cobra (*Naja bungarus*) the world's largest poisonous serpent. The venom of the mamba is of a deadly character. In South Africa there are two dangerous back-fanged colubrids, the 'Boomslang' or Tree snake and the 'Schaapstekker' (*Dispholidus typus* and *Trimacrops rhinus*). The poison of both is more virulent than that of any other snake in Africa, but their bite does not usually cause appreciable harm.

In Africa, poisonous snakes are abundant throughout the tropical and subtropical zones, but fatal accidents here are less than in India owing to the sparse population. The *Atheris*, a tree-snake closely allied to the Echis or Saw-scaled viper is found further south in Africa where vegetation is luxuriant. Other varieties of *Atheris* found here are *A. chlorechis*; *A. squamiger* and *A. ceratophorus*. South Africa has very dangerous representatives of the viperine sub-family. One of these is the Puff adder (*Causus defillipi*) which is also found in Central and East Africa. It reaches a length of 5 ft. and is as thick as a man's arm and is one of the deadliest of vipers. It is found as high up as 11,000 feet above the sea, which probably is the world's elevation record for the habitat of poisonous snake. Two large venomous, desert varieties of the horned viper, commonly known as Horned puff-adder, occur in South Africa, viz., *Bitis cornuta* and *Bitis nasicornis* the former having a beautiful coloration. This is the largest pitless viper in the world. Three other important vipers in this continent may be mentioned, they are the Night adder or Demon adder (*Cuscuta rhombatus*) and the Atractaspis species, a small burrowing gaboos both found in tropical and South Africa, and the Gaboon viper which inhabits the forest tracts of Africa.

The vast majority of poisonous snakes in America are pit-vipers. The best-known is the rattle snake, of which there are 13 known species. There are two genera (i) *Sistrurus*, with two species (*S. miliarius* and *S. catenatus*), confined to the Southern United States and Northern Mexico. Both are small, do not exceed 2½ ft. in length, (ii) *Crotalus*. The chief varieties of which are *C. terrificus*, *C. scutulatus*, *C. confluentus*, *C. durissus*, *C. horridus*, *C. carstes* and *C. adamanteus*. The tail in these snakes terminates in a series of articulated, horny cup-shaped shells, numbering 21 or more in a full grown specimen, and when disturbed or irritated, the snake vibrates these with such rapidity as to produce a rattling sound, which may be heard 60 feet away. The most dreaded species in the rattler group is the surly, quick-tempered Diamond-backed rattle snake (*C. adamanteus*) of Texas and the swamps of Florida. It is so named for the marking on the back resembling the facets of a diamond. The banded timber rattle (*C. horridus*) snake, with black longitudinal bands on its head and neck, occurs in the Eastern United States. These two are the largest members of the group and attain a length of 8 feet. *Crotalus terrificus* (cascavalla or dog-faced rattle) ranges from Mexico to Argentina. There is also a small species called the 'Side winder,' which lives in the deserts

of South Western United States. It has a pair of blunt horn-like projections above the eyes and appears to be the American replica of the horned viper of the old world.

Central America, the West Indies and Tropical South America are other regions of the New world where venomous snakes abound. The most dreaded among these is the 'Jararaca' (*Bothrops neuweidti*, boliviana or maximilian viper), a fierce and aggressive serpent about 6 feet long. It is the deadliest snake in Brazil and accounts for over 50 per cent. of the deaths from snake-bite in the country. The second most deadly snake in Brazil is *Crotalus terrificus*, which is followed by the aggressive water Moccasin (*Ancistrodon piscivorus*) or water viper and the 'Fer-de-lance' (*Lachesis lanceolatus*) whose tail ends in a horny spine, which scrapes harshly against rough objects. The giant 'Bush master' (*Lachesis mutus*) is still another terrible snake of Brazil. One other remarkable poisonous reptile of Brazil deserves notice. It is the tiny, brownish green 'Flying Reptile' which seldom exceeds 8 inches in length. It is stated that this reptile can jump long distances at a high speed. The Boa constrictor ranges from tropical Mexico to Brazil. It is the largest snake in the New world, and in the Amazon basin grows to a length of 30 ft. All boas, unlike pythons, are viviparous, the young ones being about 3 feet long at birth. Like the python, the boa is a non-poisonous snake, having no poison apparatus.

Australia is most remarkable in the character of its serpents. Viperine snakes are comparatively few and non-venomous. The snakes here consists of Elapine, snakes allied to the kraits, cobras and the coral snakes. Australia has about 105 species of poisonous snakes, all colubrids. In all there are 5 genera of a deadly type, all of which are fore-fanged. Arranged in the order of deadliness, they are: the 'Taipan' or Giant Brown Snake (*Oxyuranus maclelleni*). The Death adder (*Acanthophis porphyriacus*) maximum length 3 ft., the Tiger snake (*Notechis scutatus*) length 5½ ft., the Black snake (*Pseudochis porphyriacus*) 6 or 7 ft., and the copperhead or superb snake (*Dendrosonia superba*) 5 ft. The Taipan is the largest of poisonous snakes in Australia and grows to a length of 10 ft. or more. It is savage and aggressive. The fangs in a large specimen are about half an inch long, and at a single bite it can inject a maximum dose of 35 drops of venom, sufficient to kill 20 persons or more. There are also many species of back-fanged colubrids in Australia.

The principal varieties of pythons occurring outside India are the Reticulated python (*Python reticulatus*) of the Malay peninsula and Indo-China, which grows to a length of 30 feet; the Rock python of Tropical and South Africa (*Python sebae*), the West African python, and the Australian scrub python (*Python sphlotes*) of North Queensland. The python does not occur in Europe, but America possesses two forms allied to it, the Boa constrictor (*Constrictor constrictor*) and the Anaconda (*Eunectes murinus*).

Distribution of the Important Snakes in India

Common English Name	Zoological Name	Vernacular Name	Distribution
GROUP I—SNAKES WITHOUT ENLARGED VENTRALS—HARMLESS			
Blind snakes	<i>Typhlops braminus</i> and other species	...	Indian Peninsula, Burma and Ceylon, a few varieties in W. Himalayas, N. W. F. P. and the Punjab
GROUP II—SNAKES WITH NARROW VENTRALS—HARMLESS			
Indian python	<i>Python molurus</i>		India, Ceylon and Burma
Russell's earth snake	<i>Eryx conicus</i>	<i>Padam cootoo, manooli pambo, monadi pada</i> (Vizag) meaning earth dweller; <i>kully pambo</i> meaning mud-snake; <i>domuka</i> , two-mouthed (Hind. and Punj.)	Different parts of India
John's earth snake	<i>Eryx johni</i>	...	Do.
Iridescent earth snake	<i>Xenopeltis unicolor</i>		Burma Hills
Short-tailed earth snake of Burma	<i>Cylindrophis rufus</i>		Burma Hills
Rough-tailed earth snake	<i>Silybura ocellata</i>	Goa, Ghats to Travancore, commonest and most widely distributed

Small's brackish water snake *Cerberus rhynchops*

Do.

GROUP III—SNAKES WITH BROAD VENTRALS AND SHIELDED HEAD

(a) Sub-Group A—Harmless

Blunt-headed snake,	<i>Amblycephalus monticola</i>	Nil	E. Himalayas and Assam
No name	<i>Ablabes calamaria</i>		Himalayas, W. Ghats and Ceylon
Variegated kukri snake	<i>Oligodon subgriseus</i>	<i>Katla tutta, wanapa pam</i> (Vizag); <i>sanka</i> (Beng.)	Trans Indus; Ind. Peninsula, up to the base of Himalayas as far east as Purnea; Ceylon
No name	<i>Simotes arnensis</i>	Ceylon, Himalayas, Ind. Peninsula, N. W. F. P.
Do.	<i>Simotes cruentatus</i>	Burma
Do.	<i>Simotes cyclurus</i>	Bengal, E. Himalayas, Assam and Burma
Common wolf snake	<i>Lycondon aulicus</i> and <i>Lycond striatus</i>	Confused with krait, Common name <i>kauri-nala</i> meaning like <i>courry</i> , <i>garar</i> (U. P.); <i>soovar pambu</i> , i.e., wall snake (S. India); <i>shunguvarian</i> (Travancore)	Ceylon and Maldives, Ind. Peninsula, westward it extends throughout Punjab, Baluchistan, Persia, lower slopes of Himalayas as far east through Brahmaputra and Irrawady basin, Andamans and Nicobars, up to altitude 8,000 ft.

Common English Name	Zoological Name	Vernacular Name	Distribution
Little trinket snake	<i>Coluber helena</i>		Ceylon, Ind. Peninsula and Sindh, W. Himalayas, Burma
No name	<i>Coluber radiatus</i>		Orissa; Bengal, E. Himalayas, Assam and Burma
Dhamaṇ or rat snake	<i>Zaocys mucosus</i> and <i>Zaminis mucosus</i>	Dhamaṇ (Beng., Hind., and Mar.); <i>surey pamboṇ</i> , <i>jair potoo</i> (Tamil.); <i>mywe let pat</i> , <i>lim biri</i> (Burm).	Burma, Ceylon, Ind. Peninsula; and as far as Central India, Rajputana and Sindh; up to Sutlej valley; altitude 5,000 to 7,000 ft.
Slender dhamaṇ	<i>Zaocys korros</i>	...	Do.
No name	<i>Zaocys ventrimaculatus</i>		Baluchistan, Sindh, Punjab, Rajputana, Gujrat, W. Himalayas
No name	<i>Zaocys fasciolatus</i>		Peninsular India (to Punjab and Bengal)
No name	<i>Zaocys diadema</i>	...	N. W. India (West of Farukhabad and North of Gujrat)
Common pond snake	<i>Tropidonotus piscator</i>	<i>Neer kolee</i> or <i>neer mandalee</i> (S. India); <i>ye mywe</i> (Burma); <i>thanee pamboṇ</i> (Tamil); <i>holay havu</i> (Canarese)	Ceylon, Ind. Peninsula, Nilgiris, Conoor; up to altitude 5,700 to 6,000 ft.

Buff-striped keelback	<i>Tropidonotus stolidus</i>	Ceylon, Ind. Peninsula, Assam and Burma
Common green whip snake	<i>Dryophis mycterizans</i> and <i>D. perroteti</i>	<i>Kankotii pambu</i> , i.e., the eye plucker; <i>kumbrimuku</i> (Singhalee)	Ceylon, Annamally Hills and S. India, Burma and Siam, Western Ghats (N. Canara, Nilgiris) •
Buff whip snake	<i>Dryophis prasinus</i>	E. Himalayas, Burma, Assam and Bengal
Bronze-back tree snake	<i>Dendrophis pictus</i> , <i>dendrolaphis tristis</i> (daudin)	<i>Hal-danda</i> , i.e., like rice stalk, <i>katta kalwa</i> , i.e., black mouth (Ceylon); <i>villoni</i> (Canarese); <i>rooka</i> (Mar.); <i>bet an chora</i> (Beng.)	Himalayas, Indian Peninsula as far east as Bengal, Ceylon and Burma
Golden tree of carpet snake	<i>Chrysopelea ornata</i>	<i>Kallajin</i> (Beng. and Hind.)	Ceylon, W. Ghats (south of Goa), E. Himalayas, Assam and Burma
Golden common brown tree snake	<i>Dipsadomorphus gokool</i> , <i>Dipsadomorphus trigonatus</i>	Bengal, Assam and Burma, Ind. Peninsula (to Baluchistan and Himalayas), Ceylon
Burmese brown tree snake	<i>Dipsadomorphus multi maculatus</i>	Assam and Burma
Sind sand snake	<i>Psammophis schokari</i>	Sindh, Punjab and Baluchistan
No name	<i>Psammodynastes pulverulentus</i>	E. Himalayas, Assam and Burma

Common English Name	Zoological Name	Vernacular Name	Distribution
(b) Sub-Group B—Poisonous			
Common Indian krait	<i>Bungarus ceruleus</i> <i>Bungarus arcuatus</i>	<i>Anali</i> (Madras); <i>kattu variyan</i> <i>yenna variyan</i> (Tamil); <i>godi nagera</i> (Mysore); <i>kala</i> <i>gandatt</i> , <i>dhāman chiti</i> (Hind.)	Ceylon, Ind. Peninsula, up to Baluchistan, Almor, Indus Basin, Ganges Basin; up to altitude 5,400 ft.
Banded krait	<i>Bungarus fasciatus</i>	<i>Raj samp</i> , <i>sankni</i> (Beng.); <i>koclea krait</i> (N.W.F.P.); <i>ngan-wa</i> , <i>na t m - y u e</i> , <i>gnandawja</i> , <i>my u e - m i n</i> (Burma)	Common in Upper Burma, Assam, West of Bengal, Brahmaputra Basin, Mahanadi Basin, Irrawady Basin, south of Himalayas and south of India as far as Godavari, Tenasserim, Indo-China, South China, Malay Peninsula and Archipelago
Cobra	<i>Naja naja</i> <i>Naja tripudians</i>	<i>Nag samp</i> , <i>kala samp</i> , <i>coeri</i> <i>nag</i> , <i>sankh nag</i> (Hind.); <i>sarpam</i> , <i>moorookan</i> , <i>nalla</i> <i>pamboo</i> (S. Ind.); <i>nagoo</i> <i>kavu</i> (Mysore); <i>naga</i> <i>gokurra</i> , <i>keutah</i> (Beng.); <i>gohmanna</i> (Behar); <i>chhajhwaia</i> (N.W.F.P.); <i>chamchamar</i> (Phastu); <i>mywe howk</i> (Burma); <i>toodong sta</i> (Malaya)	Ceylon, Ind. Peninsula Assam and Burma, whole of India (from Himalayas to Ceylon, and Burma to Sind) up to altitude 6,000 ft

King cobra or hamadryad	<i>Naja bungarus</i>	Throughout India, with the exception of Ceylon (Rajputana, Sind, Punjab and Bengal) up to altitude of 7,000 ft.
Slender coral snake	<i>Callophis trimaculatus</i>	...	From South India. Deccan, Canara, Bengal to Burma Hills
Maclelland's coral snake	<i>Callophis maclellandi</i>	.. .	Himalayas as far as Kasauli to Nepal, Sikkim, Khasia Hills through Assam to Burma and South China and Formosa
Sea snakes	<i>Hydrophis coronatus</i> <i>Enhydrina valakadien</i> <i>Diatera robusta</i>	Indian Ocean

GROUP IV—SNAKES WITH BROAD VENTRALS, SCALY, AND NOT SHIELDED HEADS

(a) Sub-Group A: Pitless Vipers—Without a pit in the loreal region of the head

Saw scaled viper	<i>Echis carinata</i>	<i>Virujan, pamboo, soorootai pamboo, ratta pamboo, korattai</i> (S. India); <i>kalu havu</i> (Mysore); <i>phoorsa</i> (Bomb.); <i>afai</i> (Delhi); <i>kuppur</i> (Sind); <i>phisi</i> (N. W. F. P.); <i>ghariba</i> (Egypt)	Throughout India, from Cape Comorin to Himalayas preferably in sandy and dry areas, common in Trichinopoly. Scarce in Bengal. To the north it extends to Rajputana, Punjab, Sindh and Baluchistan to Transcaucasia. Up to the altitude of 8,000 ft.
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Common English Name	Zoological Name	Vernacular Name	Distribution
Indian daboia or Russell's viper	<i>Vipera russelli</i>	<i>Tic polanga</i> (Ceylon); <i>mandalli, kanardi virian</i> (S. India); <i>ghanas kked-chitra</i> (Bomb. & Gujrat); <i>korail</i> (Sind); <i>chandra bora, uloo bora</i> (Beng.); <i>mwe bwe</i> (Burma)	Whole of Indian Empire from Ceylon to Himalayas and from Burma to Sind. Common in the Punjab, Irrawady and Brahmaputra Basin. Up to altitudes 2,000 to 4,000 ft. and as far as 7,000 ft.
(b) Sub-Group B : Pit Vipers—With a loreal pit in the loreal region			
Common green viper (bamboo snake)	<i>Lachesis gramineus</i>	<i>Mywe sein</i> (Burma); <i>nagu kheeyo</i> (Siam); <i>ular daun</i> , i.e., leaf snake (Malaya)	Most plentifully and most widely distributed. From Malay to Burma, Andamans, Nicobar, Eastern Ghats and Nilgiris. To the west of Himalayas up to Sutlej valley. Up to altitude of 1,500 to 6,000 ft.
Green tic	<i>Lachesis trigonocephalus</i> and other species	<i>Green tic polonga</i>	Peculiar to Ceylon
Common Himalayan viper	<i>Ancistrodon himalayanus</i>	Confined to Himalayas, Khasi Hills (up to 5,000 to 12,000 ft) Lidder valley of Kashmir
Hump-nosed viper	<i>Ancistrodon hypnale</i>	Hills of Ceylon, Western Ghats of India, up to 3,000 to 6,000 ft.
Cantor's viper	<i>Trimeresurus cantoris</i> and other species	Andamans and Nicobar

ANIMALS CONFUSED WITH SNAKES

Snakes are creeping, limbless animals. Naturally other creatures having similar external characters are often mistaken for them. The lower jaws of snakes are not joined in the middle; the tongue is long, forked, protrusible and can be withdrawn into a sheath at the base inside the mouth. They have no mobile eyelids and external ears. Certain lizards which have practically no limbs can be easily mistaken for snakes. They have movable eyelids and external ear openings. Some of them also have protrusible forked tongue, but in addition possess well developed limbs. The 'blind worm' or 'slow worm' looks like a snake but it is only a limbless lizard. Certain burrowing amphibious creatures may occasionally be mistaken, but they have their vent opening at the end, whilst snakes have this opening between the tail and the rest of the body. Eels are often mistaken for sea snakes. Some of these are big and have scales, and may have no fins. Usually fish breathe by gills, but the snakes breathe by lungs. Earth-worms have the characters of being small and burrowing and have no scales on the body, which is ringed and segmented.

**TYPES OF FISH RESPONSIBLE FOR IMPACTION IN
AIR AND FOOD PASSAGES OF MAN**

ANABAS AND COLISA. These are labryrinthid fishes which are provided with organs of aërial respiration and in consequence are very lively even out of water. They are provided with series of backwardly directed spines on the gill-covers and in front of the dorsal and anal fins. These fishes when impacted in the throat with the head directed inwards are very difficult to pull out.

NESTACEMBELUS. It is a compressed eel-like fish with a series of sharp, strong and backwardly directed spines in front of the dorsal and anal fins. There are also spines on the gill-covers.

THERAPON. It is percoid fish with a number of backwardly directed spines in the vertical fins and on the gill-covers.

CYNOGLOSSUS. The scales are ctenoid and the rays of the vertical fins extends right on to the head. The form is tongue-like and liable to slip down the throat.

The treatment in cases of this type is the same as of a foreign body lodged in the food and air passages. These cases are surgical emergencies and hardly any time is available to prepare for an operation on elaborate scale. The immediate treatment consists in doing a tracheotomy as a life-saving measure.

FOOD VALUES

Proteins, Fats and Carbohydrates in grammes per ounce, Calorie-values, and Vitamin-Contents of
Common Food materials used in India.

Food-Subs	Protein	Fat	Carbo- hydrate	Calories	VITAMINS				
					A	B	C	D	E
Milk and Milk Products									
Butter	...	23.10	0.00	216	++			+	
Butter milk, unsweetened (<i>ghol</i>)	0.30	0.14	1.86	10	+		+	..	
Cheese	...	8.88	0.50	111	++	V. L			
Cream	...	5.24	1.27	55	++	+		+	
Clarified butter (<i>ghee</i>)	...	24.00	0.00	223	++		V. L.	+	
Curd, unsweetened (<i>dahi</i>)	0.40	1.00	0.80	18	++	+
Curd, fresh milk (<i>chhana</i>)	6.80	5.30	0.10	76	++		+		
Mellin's Food	...	8.20	22.70	107					
Milk, ass's	...	0.30	1.60	12	
" buffalo's	...	2.18	1.24	30	++	+	+	+	
" cow's pure	...	1.02	1.36	18	++	+	+	+	+
" bazar	...	0.60	0.70	11	++		..		
" condensed	...	2.35	15.31	92	+	+	0	..	+
" dried, whole	...				++	+	V. L.	+	+
" evaporated	...				++	+	+	+	
" goat's	...	1.13	1.21	20	++	+	+	+	
" human	...	0.42	0.75	18	++	+	+	+	
" sheep's	...	1.50	1.41	30	++	+	+	+	
" skimmed	...	0.96	1.44	10	+	+	+	+	
" whey	...	0.30	1.40	8	tr.			...	

Meat and Fish

[illegible]

FOOD-SUBSTANCES	Protein	Fat	Carbo- hydrate	Calories	VITAMINS				
					A	B	C	D	E
Shell fish									
Crabs	4.65	0.56	0.83	26					
Lobster	4.59	0.50	0.11	24					
Oysters	1.73	0.33	1.03	15					
Prawn	4.80	0.10	0.02	21					
Shrimp	7.11	0.28	0.05	32					
Eggs									
Egg (hen) whole, fresh	3.79	2.97		42	++	++		++	
" " white fresh]	3.40	tr.	0	14	0	..	0	0	++
" " yolk "	4.20	9.40	0	105	++	++	0	++	++
" (duck) whole	3.30	4.10	0	52		.			
" " white	3.10	tr.	0	13					
" " yolk	3.80	10.20	0	111		...			
Animal Fats									
Cod-liver oil ...		28.00		252	++	V.L.		++	V.L.
Fat (mutton or beef)	0.84	26.40		239	++			+	
Fish-liver oil		28.00		252	++	V.L.		++	
Halibut oil					V rich			++	
Lard		26.80		241	V.L.			..	

Vegetable Oils

Cocoanut oil ..	28'00	252	+	0	0	V.L.	..
Cocogem	28'00	252	0	0	0	.	.
Cotton-seed oil	28'00	252	V.L.	0	0
Gingelly oil	28'00	252	V.L.	0	0	0	..
Ground-nut oil	28'00	252	V.L.	0	0	V.L.	..
Linseed oil	28'00	252	V.L.	0	0
Maize (yellow) oil	..	252	+	0	0	+	++
Margarine	23'80	214	0	0	0
Mustard oil ..	28'00	252	0	0	0
Olive oil	28'00	252	V.L.	0	0	V.L.	+
Wheat-germ oil	+	++

Lentils

Broad bean (fresh)
Dal (average)
" arhar	2'66	37	-	++	+
" chana, chhola	6'50	100	+	++	0
" khassari	4'80	91
" ..	6'70	108
" kishna mung	6'80	94
" matar	6'80	94
" masoor	6'60	98
" ..	7'10	101
" ..	7'20	100
" ..	0'80	8
" soup (average)	6'40	102
" powdered (besan)	6'20	105
Gram, whole (chana, chhola)	7'60	107	+	++	0
" powdered (sattu)	6'20	98
Matar, kabi	6'20	98
Peas (dried)	1'85	28	+	++	0
Soya bean	9'60	119	+	++	0

FOOD-STUFFS	Protein	Fat	Carbo- hydrate	Calories	VITAMINS				
					A	B	C	D	E
Vegetables (including tubers, roots, etc.)									
Artichoke (<i>kathichuk</i>) ...	0.78	0.06	5.00	24	..	+	+		
Asparagus (<i>soot mooler</i>) ...	0.68	1.00	0.66	14	+	+	+		
Beans, broad (<i>seem</i>) ...	2.66	0.11	6.45	37	+	+	+		...
" French (<i>chhota seem</i>) ...	0.54	0.08	1.86	8	+	+	+		
" string (<i>barbati</i>) ...	1.00	0.40	0.80	11	+	+	+		
Beetroot (<i>chukander</i>) ...	0.34	0.08	1.75	9	✓	+	+		
Brinjal (<i>baigan</i>) ...	0.34	0.09	1.44	8	+	+	+		
Broccoli (<i>chhota phool kabi</i>) ...	0.30	tr.	0.90	5					
Brussel sprouts (<i>choke kabi</i>) ...	0.92	0.06	1.61	11	+	+	+		+
Cabbage (<i>banda kabi</i>) ...	0.39	0.03	1.27	7	+	+	+		
Carrot (<i>gajar</i>) ...	0.25	0.08	2.25	10	+	+	+		
Cauliflower (<i>phool kabi</i>) ..	0.54	0.06	1.67	9	+	+	+		
Celery (<i>shakarry</i>) ..	0.17	0.03	1.07	5		+	+		
Endive (<i>kasn leaves</i>) ..	tr.	tr.	0.70	3	+	+	+		
Fleahy roots (<i>tero</i>)	0.50	0.06	6.80	28	..	+	+		
Garlick (<i>rasoon</i>)	1.92	0.03	7.90	40	+	+	+		
Gourd, bitter, large (<i>karela</i>)	tr.	tr.	tr.		
" " small (<i>uchchhey</i>)	tr.	tr.	tr.						...
" bottle (<i>kaddu, lau</i>)	0.10	0.70	0.20	8			
" club (<i>loofah, dhundul</i>)	0.20	tr.	0.60	4					...
" snake (<i>chichunga</i>)	0.10	tr.	0.40	2					...
" sponge (<i>jhinga</i>)	tr.	tr.	tr.						...
" white (<i>chaulkumra</i>)	0.50	tr.	0.90	4					...
Green vegetables (average)	0.20	tr.	1.00	5	+	+	+		

FOOD VALUES

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[illegible]

Tapioca	tr.	24'90	102
Vermicelli	0'50	20'40	100
Wheat-flour, white (<i>maida</i>)	0'87	21'54	102
" " wholemeal (<i>atta</i>)	0'54	20'35	102
" " gluten	tr.	0'40	28
Special Foods (Bakery products)											
Akoll biscuits (<i>Huntly & Palmers, Lond.</i>)	8'00	1'70	141
Biscuit (average) do.	0'50	21'00	107
" " (digestive) do.	4'60	18'80	127
"Force" do.	0'80	20'70	100
Grape-nuts do.	0'20	22'70	110
Shredded wheat do.	0'00	21'00	99
Alpha No. 1—diabetic wafer (<i>Health Food Co., N. Y.</i>)	9'50	1'30	160
Almond biscuit (<i>Collard & Co., Lond.</i>)	13'80	1'70	174
Chocolate biscuit (casoid) do.	14'60	4'20	180
Starchless ginger biscuit do.	16'10	2'00	190
Gluten butter biscuit (<i>G. Van. Abbott & Sons, Lond.</i>)	9'40	4'70	154
Walnut biscuit do.	16'20	3'40	189
Nuts and Seeds											
Almond (<i>kagji badam</i>)	15'96	4'30	182	...	V.L.	++
Brazil nut	20'00	2'10	216	...	+	+
Chestnut	16'20	12'60	210	+
Groundnut (<i>mungphali, cheena badam</i>)	10'92	6'90	155	...	V.L.	+
Linseed	9'50	7'60	142	...	++	+
Plantain (<i>pesta</i>)	16'20	4'80	198	+
Walnut (<i>akhot</i>)	19'92	3'96	211	...	V.L.	++
Other nuts	16'50	3'60	183	...	V.L.	++

Food-Substns	Protein	Fat	Carbo- hydrate	Calories	VITAMINS				
					A	B	C	D	E
Fresh Fruits									
Apple	0.09	0.06	8.54	15	+	+	+
Banana, plantain	0.45	0.08	2.26	11	V.L.	..
Bael (<i>Egle marmelos</i>)	0.20	0.20	4.50	21
Blackberry (<i>kala jam</i>)	0.40	0.20	1.00	8	..	+	+
Cocoanut water	0.40	..	0.70	5
" kernel (<i>warkel</i>)	1.61	14.31	7.90	167	+	+	0
Cucumber (<i>khirra, sasha</i>)	0.17	0.02	0.57	8	..	+	+
Grape	0.17	0.08	3.93	17	..	+	V.L.
Guava	0.37	0.20	2.27	12	..	+	+
Jack-fruit (<i>kantal</i>)	0.30	0.10	5.30	24
Lemon	0.14	0.14	0.83	5	+	+	+
Lichee	0.84	0.07	1.30	12	..	+	+
Mango (ordinary)	0.04	0.22	5.20	23	+	..	+
" Bombai or langrah	0.50	0.20	5.10	26	+	..	+
Melon (<i>footee</i>)	0.40	..	1.10	6
" musk (<i>kharbaja</i>)	0.60	..	1.30	10
" water (<i>karbaj</i>)	0.11	0.06	1.30	9	+
Orange	0.25	0.08	0.10	12	+	+	+	..	+
Papaya	0.16	..	0.10	1	+	+	+
Peach	0.19	0.08	2.66	12	+	+	+
Pear	0.09	0.08	2.29	10	..	+	+
Pineapple (<i>anaras</i>)	0.11	0.09	2.75	12	+
Plum	4.10	17	+	..	+
Pomegranate (<i>bedana</i>)	0.30	tr.	2.19	10	..	+	+
" (<i>dalim</i>)	0.18	..	0.19	2	..	+	+
Pomelo (<i>batabi nimbu</i>)	0.20	..	2.10	10

Raspberry	...	0'47	0'28	3'53	18	...	+	+	+
Roseberry (<i>golab jam</i>)	...	'40	...	1'40	7	+	...	+	+
Strawberry	...	0'20	0'10	2'30	11	...	+	+	+
Sugarcane	...	0'42	0'16	6'20	28	...	+	+	+
Water nut (<i>singara, panifal</i>)	...	0 30	tr.	5'70	24
Dried Fruits											
Apricot (<i>khobani</i>)	...	1'57	0'09	14 04	63	0	0
Currant	...	0'48	0'09	11'89	50	...	0	0	0
Date	...	0'45	0'08	19'73	81	+	+	+	0
Fig	...	0'56	0'14	15'99	67	...	+	+	0
Prune	...	0'85	0'09	11'45	50	+	+	+	0
Raisin	...	0'62	0'09	17'32	73	...	+	+	0
Tamarind	...	0'39	...	8'89	37	+	+
Sweets											
Cake (sponge)	...	18'70	1'70	3'00	112	+	+
" fruit	...	18'20	1'60	3'70	117
Honey	...	0'11	...	20'21	81	v.L.	v.L.	v.L.	0
Jaggery (<i>goor</i>)	...	0'08	...	25'00	100	0	v.L.	0	0
Jam	...	0'06	...	19'81	79	0	0	0	0
Marmalade	...	0'06	...	19'41	78	0	v.L.	0	0
Pastry (cream)	...	0'40	3'20	14'40	91
" (custard)	...	1'20	1'70	7'40	51
Pickle	...	0'31	0'11	1'13	7
Sandesh (best)	...	5'40	6'00	12'00	124	0	0	0	0
Sugar (brown)	26'89	108
" (white)	28'30	113
Treacle	...	0'06	...	16'95	68	0	0	0	0	...	0

FOOD-STUFFS	Protein	Fat	Carbo- hydrate	VITAMINS				
				A	B	C	D	E
Miscellaneous								
Boiled rice (<i>bhat</i>)	1.40	0.30	16.70					
Chapati	2.60	1.00	19.60					
Cocoa	5.10	7.50	10.60	+			-	
Coffee			...	0	0	0		
Green grass				++	++	++		
Infant's food (tinned)	3.50	0.98	21.56					
Leochi (fried in <i>ghee</i>)	2.10	6.40	14.20					
Paratha (cooked in <i>ghee</i>)	2.30	5.00	14.40					
Pepper	4.30	2.41	17.33					
Soup, chicken	2.90	0.20	0.60					
" pea	1.40	1.90	3.10					
" tomato	0.50	0.80	1.50					
Tea				0	0	0		
Yeast, fresh	4.00	0.56	2.49		++		0	
+++ mean rich in ; ++ mean moderately rich in ; + means some or poor in ; 0 means none ; V.L. means very little , tr. means trace One ounce equals 28.3 grammes.								

CALORIE VALUES OF FOOD-STUFFS

1 gramme carbohydrate yields 4.1 calories.

1 gramme protein yields 4.1 calories.

1 gramme fat yields 9.3 calories.

1 c.cm of alcohol yields 5.6 calories.

Mineral Constituents of Common Food-Stuffs

Milk and Milk Products				Ca	P	Fe	Cu
Butter	0'015	0'017	2'0	...
Buttermilk	0'105	0'087	2'5	...
Cheese (Swiss)	0'999	0'845	12'5	1'8
Cream	0'090	0'080	2'2	...
Milk, whole	0'120	0'098	2'4	0'2
„ skim	0'122	0'096	2'5	0'2
„ evaporated	0'250	0'200	5'8	1'2
„ condensed	0'800	0'285	6'0	1'0
„ dried	0'920	0'710	1'5	1'5
Meat, Fish, etc.							
Bacon	0'006	0'108	24	5'0
Beef, steak	0'012	0'216	80	1'0
Chicken	0'012	0'282	82	8'5
Duck	0'010	0'200	28	5'0
Ham	0'012	0'215	80	...
Liver (beef)	0'017	0'218	79	21'5
Mince meat	0'085	0'175	80	...
Mutton (leg)	0'010	0'270	80	4'0
Pork (chops)	0'010	0'180	25	8'1
Turkey	0'080	0'420	45	1'8
Veal (cutlet)	0'018	0'228	80	2'5
Fish, cod	0'012	0'120	6	5'5
„ halibut	0'020	0'200	10	2'8
„ salmon	0'025	0'250	12	2'0
Lobster	0'018	0'188	9	7'0
Oyster	0'052	0'155	45	80'8
Shrimp	0'096	0'292	27	...
Eggs							
Egg (hen) whole	0'067	0'180	80	2'8
„ „ white	0'015	0'014	1	...
„ „ yolk	0'187	0'524	86	1'2
Vegetables							
Artichoke	0'081	0'087	20'0	8'1
Asparagus	0'025	0'089	10'0	1'4
Beans, dry	0'160	0'471	95'2	6'9
„ green	0'046	0'052	9'8	1'0
Beetroot	0'029	0'089	28'6	1'9
Beet leaves	85'5	0'9
Brinjal	0'011	0'084	5'0	1'0
Cabbage	0'045	0'029	8'5	0'5
Carrot	0'056	0'046	6'4	0'8
Cauliflower	0'123	0'061	9'4	1'4
* Celery	0'078	0'087	6'2	0'1
Lettuce	0'043	0'042	7'0	0'4
Mushroom	0'017	0'108	81'0	17'9

Ca—Calcium ; P—Phosphorous ; Fe—Iron ; Cu—Copper.

Vegetables—contd.	Ca	P	Fe	Cu
Onion	0'084	0'045	4'0	0'8
Parsnip	0'059	0'076	10'7	1'2
Peas, dry	0'084	0'400	57'0	14'0
„ green	0'028	0'127	21'0	2'4
Pepper, green	0'006	0'026	4'0	1'0
Potato	0'014	0'058	9'1	1'7
„ (sweet)	0'019	0'045	9'0	1'5
Pumpkin	0'028	0'059	9'3	0'8
Radish	0'021	0'029	8'3	1'6
Rhubarb	0'044	0'081	7'6	0'5
Sauerkraut	0'040	0'025	4'0	0'4
Spinach	0'067	0'068	38'5	1'2
Tomato	0'011	0'026	6'0	0'7
Turnip ...	0'064	0'046	6'2	0'9
Cereals and Cereal Products				
Barley, pearled	0'020	0'181	20	4'0
Bread, white	0'027	0'098	9	3'4
„ brown	0'050	0'185	30	5'0
„ rye	0'024	0'148	16	
Corn meal	0'018	0'190	9	2'0
Flour, white	0'020	0'092	10	1'7
„ rye	0'018	0'289	18	4'2
„ buckwheat	0'010	0'176	12	
Macaroni ...	0'022	0'144	12	
Oatmeal	0'069	0'392	38	5'0
Rice, white	0'009	0'096	9	1'9
Tapioca ..	0'023	0'090	16	
Wheat, whole	0'045	0'428	50	6'0
„ bran	0'120	1'215	78	11'7
Fresh Fruits				
Apple	0'007	0'012	5'0	1'0
Banana ...	0'009	0'081	17'6	2'1
Blackberry	0'017	0'084	10'0	1'6
Cherry ...	0'019	0'081	4'0	1'4
Cucumber	0'016	0'088	8'8	0'6
Grape	0'019	0'081	7'8	0'9
Grape fruit	0'021	0'020	2'7	0'3
Lemon ..	0'086	0'022	6'0	0'4
Orange ..	0'045	0'021	5'2	0'8
Peach ...	0'016	0'024	8'5	0'9
Pear	0'015	0'026	8'5	1'0
Pineapple	0'018	0'028	8'7	0'7
Raspberry	0'049	0'052	8'8	1'4
Strawberry	0'041	0'028	6'8	0'2
Dried Fruits				
Apricot ...	0'014	0'025	25'0	1'3
Date ...	0'065	0'056	36'0	3'8
Fig ...	0'182	0'116	29'0	3'5
Prune ...	0'054	0'105	29'0	4'1
Raisin ...	0'064	0'182	29'0	2'0

				Ca	P	Fe	Cu
Nuts							
Almond		0'289	0'465	40	12'1
Brazil nut	40	18'9
Chestnut, fresh		0'084	0'098	41	6'0
Cocoanut, dry		0'059	0'155	20	6'9
Pistachio	79	12'0
Walnut	0'060	0'860	21	10'9
Miscellaneous							
Cake (sponge)		0'078	0'221	88	...
Chocolate (unsweetened)		0'092	0'455	27	25
Cocoa		0'112	0'709	27	80
Honey		0'004	0'019	7	2
Molasses		0'211	0'044	73	20
Yeast (fresh)	0'011	0'445	8	..

MINERAL NUTRIENTS

Their Functions in the Body, Deficiency Symptoms and Dietary Sources

CALCIUM (Ca).

Functions. Building of bones and teeth; Coagulation of blood; Ion balance; Heart, nerve and muscle functions; Enzyme activation; Essential for lactation.

Deficiency symptoms. Poor development of bones and teeth; Rickets; Brittle bones; Dental caries; Excessive bleeding; Tetany; Heart atony; Hyperirritability.

Dietary sources. Foods, see page 1637. *Chemical compounds*—calcium lactate, calcium gluconate, calcium glycono-phosphate, dicalcium phosphate.

CHLORINE (Cl).

Functions. Regulation of osmotic pressure in blood and tissues; Aid to digestion; Essential to normal gastric secretion; Activation of enzymes.

Deficiency symptoms. Digestive disturbances; Loss in body weight; Poor water retention; "Salt hunger"; "Miner's cramps"; Achlorhydria,

Dietary sources. Bread, cheese, oysters, ham, sauerkraut, banana, bran, buttermilk, cabbage, celery, cocoanut, dates, eggs, endive, fish, molasses, potato, spinach, tomato. *Chemical compounds*—sodium chloride (common salt).

***COPPER (Cu).**

Functions. Essential for the utilization of iron in synthesizing haemoglobin (it is doubtful whether this action of copper is of any therapeutic importance); Aids tissue respiration.

Deficiency symptoms. Aæmia; Restricted growth; Impaired respiration; Poor utilization of iron; Weakness.

Dietary sources. Foods, see page 1637. *Chemical compounds*—copper sulphate, copper pyrophosphate. (Copper is poisonous in larger amounts).

IODINE (I).

Functions. Thyroxine formation; Functioning and size of thyroid gland; Regulation of basal metabolism; Protection against goiter.

Deficiency symptoms. Enlarged thyroid gland (this may be followed by either too much or too little thyroxine secretion—basal metabolism becoming too high or too low). Subnormal basal metabolism; Lowered mental activity; Nervous disturbances; Over-weight.

Dietary sources. Codliver oil, fish, halibut, lobsters, oysters, shrimp, barley, beans (green), bran, butter, carrots, cherries, oats, spinach. *Chemical compounds*—sodium iodide, potassium iodide. "Iodized salt" (0.02 per cent. NaI). (The iodine content of vegetables and fruits varies greatly with the locality).

IRON (Fe).

Functions. Hæmoglobin formation; Oxygen transport; Tissue respiration; Development of blood cells; Normal complexion.

Deficiency symptoms. Anæmia; Low vitality; Decreased hæmoglobin and red blood cells, Pallid complexion; Retarded growth.

Dietary sources. Foods, see page 1637. *Chemical compounds*—ferrous sulphate, iron citrate.

MAGNESIUM (Mg).

Functions. Necessary for muscle activity; Ion balance; Laxative effect; Enzyme activation.

Deficiency symptoms. Nervousness; Digestive disturbances; Retarded growth; Vasodilation; Spasticity; Rapid heartbeat; Arrhythmia.

Dietary sources. Almonds, barley, beans, bran, brussels sprouts, chocolate, corns, peanuts, peas, prunes, raisins, rye, spinach, walnuts, banana, beans (green), beef, beets, blackberry, cabbage, carrots, cheese, cocoanut, currants, dates, figs, fish, milk, oatmeal, oysters, parsnips, potatoes, raspberry, rice. *Chemical compounds*—magnesium citrate, magnesium sulphate (Epsom salts), magnesium hydroxide (milk of magnesia).

MANGANESE (Mn).

Functions. Important for normal growth; Helps tissue respiration.

Deficiency symptoms. Subnormal growth; Poor tissue respiration.

Dietary sources. Banana, beans, beets, bran, chocolate, peas, leafy vegetables, whole grain. *Chemical compounds*—manganous chloride, manganous sulphate.

PHOSPHOROUS (P).

Functions. Building of bones and teeth; Activation of enzymes; Essential for metabolism of carbohydrates and fats; Buffer action in blood and muscles; Essential constituents of all cells.

Deficiency symptoms. Poor development of bones and teeth; Retarded growth; Perverted appetite; Loss in weight; Weakness; Rickets.

Dietary sources. Foods, see page 1637. *Chemical compounds*—glycero-phosphates, lecithin, dicalcium phosphate, disodium phosphate.

POTASSIUM (K).

Functions. Normal growth; Ion balance; Muscle function; Buffer action; Osmotic pressure in cells and fluids.

Deficiency symptoms. Nerve disorders; Irregular heart action; Poor muscular control; Loss in body weight; Poor digestion.

Dietary sources. Beans, bran, molasses, olives, parsnips, potatoes, raisins, spinach, apricots, asparagus, banana, beef, beets, cabbage, carrots, cauliflower celery, chocolate, cocoa, cocoanut, currants, dates, figs, grapes, lettuce, milk, mushrooms, nuts, peaches, peas, pineapple, plums, prunes, rhubarb tomatoes, turnips. *Chemical compounds*—sodium potassium tartrate, potassium sulphate, potassium chloride, potassium acid tartrate.

SODIUM (Na).

Functions. Regulation of osmotic pressure in cells and fluids; Ion balance in tissues; Buffer action in blood stream.

Deficiency symptoms. Nerve disorders; Irregular heart action; Poor muscular control; Loss in body weight; Poor digestion.

Dietary sources. Blood, bread, cheese, crackers, oysters, spinach, wheat germ, beef, beets, bran, carrots, celery, eggs, milk, musk-melon, olives, pumpkin, raisins, strawberry, turnip. *Chemical compounds*—sodium chloride, sodium bicarbonate, disodium phosphate, sodium potassium tartrate.

SULPHUR (S).

Functions. Required as cystine or cysteine or their combinations for the synthesis of body proteins (thiosulphate feeding and high protein diets often relieve eczema and dermatitis); When oxydized to sulphate, plays an important role in ion balance of tissues.

Deficiency symptoms. Dermatitis; Retarded growth (restricted growth and death result from a prolonged deficiency of cystine or cysteine-containing proteins in the diet. An adequate supply of good protein leads to the formation of inorganic sulphate in the body, as a result of tissue oxidation of cystine).

Dietary sources. Beans, bran, cheese, cocoa, eggs, fish, meat (lean), nuts, peas, bread, brussels sprouts, cabbage, cauliflower, macaroni, oats, onion, oysters, turnip, wheat. *Chemical compounds*—magnesium sulphate, sodium sulphate.

VITAMINS

Biological and Chemical Properties, and Distribution

Vitamin A (Antiophthalmic). See page 162.

Positive effects. Essential for normal vitality of epithelial cells;

Increases resistance to infections; Promotes growth; Increases life span; Aids in maintaining normal glandular functions.

Deficiency symptoms. *Mild.* Poor resistance to infections; Retarded growth; Lack of vigor; Poor appetite; Decreased Lactation; Dry skin; Diarrhoea; Night blindness. *Extreme.* Xerophthalmia; Infections through epithelia: eyes, tear ducts, tongue, alimentary tract, ear canal, sinuses, bladder, kidneys; Sterility; Weakness; Loss in weight; Atrophy of glands; Calculi in kidneys and bladder.

Chemical Properties. A sterol (alcohol of high molecular weight) $C_{26}H_{50}O$? Carotene ($C_{40}H_{56}$), the yellow colouring matter of most vegetables and fruits, is converted in the body to vitamin A (colourless); Heat stable; Moderately sensitive to Oxydation; Stable to acids and alkalis; Soluble in oils and fats; Almost insoluble in water, Gives an intense blue colour with $SbCl_5$.

Dietary sources. See 'Food Values', Page 1626.

Vitamin B Complex.

Vitamin B was originally regarded as a single substance. Recently, however, this vitamin has been divided into at least five factors, with the possibility of a sixth, and is called Vitamin B Complex. The table on page 1643 indicates the general view at the present time of the six factors in Vitamin B Complex. It is very doubtful whether or not all these vitamins are necessary for the human subject. From the general point of view the vitamin has been divided into two substances, B_1 and B_2 . In food-stuffs the different factors are often associated with each other.

Vitamin B_1 (Antineuritic). See page 192.

Positive effects. Essential for normal condition and functioning of nerve tissue; Stimulates appetite; Promotes growth; Aids digestion and assimilation; Related to lactic acid metabolism.

Deficiency symptoms. *Mild.* Weakness; Digestive disturbances; Poor appetite; Retarded growth; Slow heartbeat; Nervousness; Decreased peristalsis; Poor assimilation and lactation. *Extreme.* Beriberi; Polyneuritis; Paralysis; Atrophy of glands; Loss in weight; Intestinal infections; Convulsions; Gastric atony; Head retraction; Atrophy of musculature.

Chemical properties. Low molecular-weight; Stable towards dry heat, but destroyed by autoclaving; Soluble in water; Insoluble in oils and fats; Basic nitrogen compound; Readily absorbed by charcoal and Fuller's earth.

Dietary sources. See 'Food Values', Page 1626.

Vitamin B_2 (G or PP) (Antipellagric). See page 194.

Positive effects. Improves growth; Promotes general health; Prolongs active life-span.

Deficiency symptoms. *Mild.* Digestive disturbances; Impaired growth; Lack of vigor; Shortened life-span; Poor lactation. *Extreme.* Pellagra (other factors besides vitamin B_2 may be involved in pellagra);

Vitamin B Complex

The following Table indicates the general view at the present time of the six factors in Vitamin B also known as Vitamin B complex

Factor	Remarks on Designation	Observations from Animal experiments	Characteristic Properties
B ₁	The "Antineuritic vitamin" (Eijkmann) 1897. Torulin (Peters) Anti-beri-beri vitamin. B.P. factor (Goldberger). Vitamin F (Sherman).	Required by rat for growth. Deficiency causes condition known as "poly-neuritis" or experimental "beri-beri" in rats, dogs and pigeons.	Unstable to alkali. Relatively stable to acid.
B ₂	The Antidermatitis factor or Antipellagra vitamin (Goldberger) 1926. P.P. factor (Goldberger). Vitamin G (Sherman). Possibly the vitamin D of Funk and Lecoq.	Required by rat for growth. A deficiency produces in rats and dogs abnormal condition of the skin and tissues resembling to some extent pellagra. Apparently not necessary for pigeons.	Stable to acids. Moderately stable to alkalis. Thermostable in neutral solution.
B ₃	A factor described as the "third pigeon factor" by Williams and Waterman 1927. Not identical with the B ₃ of Reader now designated B ₄ .	Not required for growing rats but necessary for pigeons.	Thermolabile.
B ₄	First described by Reader and formerly designated B ₃ by her. Probably identical with the "vitamine d'utilisation nutritif" of Lecoq.	Required by rat and also, probably by pigeons.	Unstable to alkalis.
B ₅	Described by Carter, Kinnersley and Peters.	Probably required for the growth of rats.	Thermostable.
B ₆ (or Y)?	Chick and Copping	Rats	Stable to heat and alkali.

Dermatitis; Weakness; Break-down of central nervous system; Cataract; Loss of hair; Ulceration of tongue; Loss in body weight of intestines; Atony.

Chemical properties. Soluble in water; Stable to heat; Fairly stable to oxidation, acids, and alkalis; Thought to be identical with or similar to lactochrome.

Dietary sources. See 'Food Values', page 1626.

Vitamin C (Antiscorbutic). See page 196.

Positive effects. Essential for normal conditions of endothelial cells; Favours good teeth development; Improves appetite; Stimulates growth; Essential to tissue respiration.

Deficiency symptoms. *Mild.* Tender joints; Retarded growth; Defective teeth; Poor resistance to infections; Weakness; Restlessness; Digestive disturbances, Weakened blood capillaries; Poor lactation; Lesions in endothelial tissue; Headache. *Extreme.* Scurvy; Hæmorrhages, Swollen joints and gums; Paralysis; Loose teeth; Beaded ribs; Fragile bones; Sterility; Respiratory and intestinal infections; Lesions in bone marrow and teeth; Hypertrophy of adrenals. Atrophy of musculature.

Chemical properties. Ascorbic acid ($C_6H_8O_6$); Very sensitive to alkalis and oxidation; Fairly stable in weak acid solutions; Generally destroyed by drying and by cooking exposed to air, and not by cooking in steam; Soluble in water; Insoluble in oils; Strong reducing agent; 2,6-Dichlorophenol indophenol serves as a good titrating agent.

Dietary sources. See 'Food Values', page 1626. Cooking in open vessel may readily destroy most of the vitamin C value of foods, except the acid juices.

Vitamin D (Antirachitic). See page 186.

Positive effects. Regulates metabolism of lime and phosphorous; Essential to growth of bone and development of teeth; Favours good body form, Controls blood calcium level.

Deficiency symptoms. *Mild.* Poor assimilation of lime and phosphorous; Poor deposition of lime and phosphorous in teeth and bones; Restlessness; Lack of vigor; "Bow legs"; Low blood-calcium and phosphate; Predisposition to dental caries. *Extreme.* Rickets; Softened bones; Enlarged joints; Curved spine; "Pigeon breast"; Beaded ribs; Retarded growth; Severe loss of lime and phosphorous; Lesions in bones and teeth.

Chemical properties. Formula $C_{27}H_{45}O$; Formed by irradiation of ergosterol (the vitamin is also formed in human and animal bodies when the skin is exposed to direct sunlight or ultraviolet radiation); Stable to heat, alkalis and acids; Fairly stable to oxydation; Soluble in oils and fats; Insoluble in water.

Dietary sources. See 'Food Values,' page 1626.

Vitamin E (Antistatility). See page 190.

Positive effects. This vitamin is so widespread and stable that a significant deficiency in human diets is unlikely.

BALANCED DIET

BALANCED DIET
*FOR VEGETARIANS

(Prepared by the Bombay Presidency Baby and Health Week Association)

No.	GROUP	FOOD-STUFFS	AT MINIMUM COST PER MAN				AT MODERATE COST PER MAN			
			PER DAY		PER MONTH		PER DAY		PER MONTH	
			Quantity	Calories	Quantity	Cost	Quantity	Calories	Quantity	Cost
			Oz.		Oz.	Rs. a. p.	Oz.		Oz.	Rs. a. p.
1	Rice	Rice broken (Kari)	11	1145	330	0 7 5
2		" bran (fresh rice polishings)	1	...	30	0 0 8	0.75	...	32	0 0 5
3		" polished	4	452	120	0 8 8
4		" unpolished	6	594	180	0 8 7
5	Other cereals	Wheat (Bajri) (Burmah millet), Jowar	5	545	150	0 6 2	8	872	240	0 9 11
6	Pulses	Lentils (masoor), Tur dal (pigeon peas),
7		Peas and Beans
8		Whole horse grams
9	Soya beans	Sweet Oil (natural coconut oil, etc.)	2	202	60	0 2 6	1.2	121	34	0 1 8
10	Vegetable oils	Pure ghee or butter	0.75	51	24	0 0 10	0.8	61	24	0 0 10
11	Animal fats	Skim milk (10 oz. skim milk=1 oz. dried)	1.2	178	45	0 2 5	1	118	34	0 1 7
12	Milk	Groundnut cake
13	Oil cake	Jaggery (gour) or sugar
14	Sugar	Tomato, radish, carrot, onion, potato, etc.
15	Leafy vegetables	Spinach (phata), cabbage, brinjel, etc.	3.0	...	90	0 3 0	6	...	180	0 7 0
16	Condiments	Chillie, ginger, pepper, cloves, anhi, etc.	0	38	180	0 6 6	6	38	180	0 6 6
17	Salts	Sundries like hot drinks, fruits, sweets, etc., taken on occasions	0 2 6	0 2 6
18	Miscellaneous	Fire-wood or coke and coal	0 7 1	0 8 2
19		Total	48.75	6 0 0	67.50	7 0 0

*For NON-VEGETARIANS substitute meat, fish, egg, etc., for milk. Condiments may also be omitted.
Costs have been calculated at wholesale rates in Bombay for a family of five members.

WINES AND OTHER BEVERAGES

The energy value of spirituous liquors is not always confined to their alcoholic content. The carbohydrate contained in them may be either sugar or starch, the former is fruit sugar in natural wines, or cane sugar which is added to the liquors. Malt liquors contain the unfermented portion of the malt sugars, chiefly malto dextrins and dextrin. The spirits are carbohydrate-free, the dry wines contain only a negligible quantity, while the sweet wines have an appreciable amount, and so too have the port and sherry group. Liqueurs are exceedingly rich in cane sugar, while malt liquors owe their fat forming qualities as much to carbohydrate as to alcohol.

Composition of a Few Common Alcoholic Beverages

CHAMPAGNE. Alcohol (12 to 14 per cent.), sugar (6 to 24 gr. per oz.), energy value (22 calories per oz.).

PORT. Alcohol (20 to 23.2 per cent.), sugar (16 to 36 gr. per oz.), energy value (35 calories per oz.).

BURGUNDY. Alcohol (9 to 13 per cent.), sugar (nil, or just a trace), energy value (18 calories per oz.).

SHERRY. Alcohol (15.4 to 24.7 per cent.), sugar (0 to 18 gr. per oz.), energy value (31 calories per oz.).

BRANDY. Alcohol (40 per cent.), energy value (64 calories per oz.). The energy value of other spirituous liquors such as Whisky, Gin and rum, is the same as that of brandy.

MALT LIQUORS (Beer and stout). Alcohol (4 to 6 per cent.).

Beers—12 calories per oz.

Stout—13.5 calories per oz.

Composition of Other Beverages

TEA (0.5 oz. to 1 pint water). Carbohydrate 0.6 per cent.

COFFEE (1 oz. to 1 pint water). Carbohydrate 0.7 per cent.

COCOA (0.5 oz. to 1 pint water). Carbohydrate 1.1 per cent.

COCOA (0.5 oz. to 1 pint milk). Carbohydrate 6.0 per cent.

COCOA (sweetened, not as prepared for drinking). Protein 18.3 per cent.; fat 26.7 per cent.; carbohydrate 37.5 per cent.; calories 464.

CARBONATED DRINKS (bottle soda, sarsaparilla, brich beer, root beer, * gingerale). Carbohydrate 8.0 per cent.

CHOCOLATE (not as prepared for drinking). Protein 12.4 per cent.; fat 52.2 per cent., carbohydrate 24.8 per cent.; calories 619.

Principal Food Grains of India

CEREALS

The grain of the grasses is a complete fruit; in a few familiar cases (barley) it commonly retains, as an additional and firmly attached covering, a pair of paleæ. In all cases where these floral envelopes adhere to the winnowed grain they must be removed by some mechanical operation before the cereal can be used as human food; the harshness of these envelopes as well as the indigestibility of the large amount of fibre which they contain necessitate this treatment.

A considerable and often excessive proportion of starch is a characteristic feature of the composition of these grains.

Avena sativa Linn. Oats; (Hind.—Wiláytí-jau, jaf). Cultivated in some parts of India. Almost perfectly adjusted food so far as chemical composition and ratio of nutrients are concerned. Contains nitrogenous substance 10.25, starch 50 to 60, and fat 5.27 per cent.; calories per ounce 115; little Vitamin A, moderately rich in B.

Eleusine coracana Gaertn. (Sans.—Rájika, rági; Hind. & Beng.—Marúa). Several cultivating varieties of which var. *stricta* Roxb. often surprisingly productive. Widely cultivated in Himalayan districts, the Punjab, N. W. F. P., Oudh, Bihar, Bengal, Madras, Mysore (where it forms food for four-fifths of population), and Bombay. Largely eaten by labouring and poorer classes; somewhat difficult of digestion, produces flatulence, astringent; in Darjeeling fermented liquor is prepared from grains. Husked *rági* contains albuminoids 7.3, starch 73.2, and oil 1.5 per cent.

Hordeum vulgare Linn. (Syn.—*Hordeum sativum* Pers.)—Barley; (Hind.—Jav, jao; Beng.—Jab). Six sided variety usually grown in India; by far the largest quantity grown in N. W. F. P. and the Punjab; to a much less degree in Ajmer, Merwara, Bombay, C. P., and Madras; generally sown in October and November, reaped in February and April. As prepared for food in India, generally considered rather difficult of digestion. Contains protein 10, starch 56 to 66, and fat 1.87 per cent.; calories per ounce 100; little Vitamin A but moderately rich in B.

Oryza sativa Linn. The Rice; (Sans.—Dhanya; Hind.—Chaul, cháwal—cleaned rice; Beng.—Dhán; Tam.—Arisi). Staple food of great majority of Indians, especially in Madras, Bengal, Assam, Bihar, Orissa, Bombay, Kashmir, and Burma. Good number of varieties in cultivation. Several kinds of rice found in the market and named after some prominent character; thus there is *Patni*, from centre of export; *Peshawari*, because handled by up-country merchants; *Básmati*, fine flavoured, etc. Some are coarse grained, short and plump like the Burma rice, or long, plump and coarse grained like *dest* or indigenous rice, e.g., *Aus*, *Nagri*, *Patni*. Others are finer grade rice with long and fine fruit like *dadhani*, or long and medium such as *Peshawari* and *Kamini bhog*, etc.; these are more digestible than coarse grained ones.

RICE PREPARED FOR MARKET IN VARIOUS WAYS:—

Husks are prepared for removal from paddy or *dhán* in three ways:

(1) *Atap* or sun-dried rice prepared by drying the paddy in the sun. Separation of the husk is facilitated by sprinkling cold water or soaking the paddy in the same prior to drying in the sun. This method does not destroy enzymes of the grain. Fine, middle, and coarse grades of rice prepared in this way are available under different vernacular names.

The coarse grade varieties are generally implicated with beri-beri and epidemic dropsy.

(ii) *Siddhā* or parboiled rice prepared by soaking paddy in large vessels and then boiling it over slow fire. This parboiled rice is dried on platforms before husking. Most enzymes are killed, and surface proteids in the grains coagulate during this operation. Rices prepared in this way are also available in the above mentioned grades of which the middle and the coarse grades are implicated with epidemic dropsy.

(iii) *Balam* rice consists of paddy husked after sprinkling hot water or steeping in the same. Heat to which the paddy is subjected is not sufficient to kill the enzymes or to coagulate proteids; takes less time in swelling the grain than in (i). This can be had only as the middle grade variety and is implicated with epidemic dropsy.

Removal of husks is carried out in 2 ways:—

(a) *Anchattā*, by hand: with wooden pestle and mortar, or it being beaten on a platform with wooden beam (*dhenki*). Hand pounding leaves a good deal of pericarp on the grains. (b) *Kalchattā* or machine removal carried out in mills. In the first place the husks are removed by passing the grain through milling stones, screens, and winnowing machines. The kernels are then decorticated, and the outer cuticle with much of the gluten layer of the grain and the embryo are removed; this constitutes the rice bran or meal. This rice is known as unpolished rice.

Finally the grains are polished. In this process a film of gluten and starch cells is removed, and the fine powder thus obtained is technically called rice polishings; the polished grains are then screened in various grades and sizes.

The terms *atap*, *siddhā*, etc., do not denote the different types of rice but the different modes of preparation that are followed before it is sent out to the market.

Thus parboiled rice kills living cells and enzymes; machine milling and polishing removes embryo and delicate starch cells and exposes raw surfaces to bacterial and fungal attack.

Old or seasoned rice is preferred to new; the common habit of throwing away water in which it has been boiled is not good; it involves loss of mineral matter in which rice is notoriously deficient; steam cooking is advocated. Rice eating people of the poor class suffer from dyspepsia, diarrhoea, dysentery, and anaemia through imperfectly cleaned rice; polished rice is considered to be a main cause of beri-beri, due to deficiency of Vitamin B. Composition varies in different forms; on the whole poor in proteins and fats; on average protein 7, starch 76, and fat 1.28 per cent.; calorific value 1630 (per lb.), of boiled rice 525.

Panicum colonum Linn. 'Shama' Millet; (Hind.—Sawānk; Beng.—Shama; Tel.—Wundn). Abundant throughout plains, ascending to 6,000 ft. in Himalayas; in parts of the Punjab also cultivated. Grain collected for food in many parts, especially Northern India, by the poor. Husked seeds contains nitrogenous substance 11.8, starch 74, and fat 3.12 per cent.

P. miliaceum Linn. The Indian Millet; (Hind.—Chenā; Beng.—Chinā; Tam.—Varagu). Largely grown in many parts of India, especially Purniah district. Contains protein 10.6, starch 60.2, and fat 3.89 per cent.

* *P. miliare* Lamk. The Little Millet; (Hind.—Kutkī; Beng.—Gondulā; Tam.—Shamai). Cultivated to some extent in many districts, grown in the Punjab up to Kheri Pass, Nepal, and Central India. Mostly consumed by poor classes. Contains albuminoids 9.1, starch 69.0, and oil 3.6 per cent.

Paspalum scrobiculatum Linn. The Koda Millet; (Hind.—Kodá, kodaká; Beng.—Kodoá, dhán; Tel.—Allu). Cultivated in many parts of India during rainy season. Used by large number of Indians especially in the districts of Mirzapur, Gorakhpur, Patna, Shahabad, Saran, Bhagalpur, Purniah, and Santal Parganas. Husked grains contain albuminoids 7.0, starch 77.2, and oil 2.1 per cent., not considered wholesome diet; unless special precautions are taken, it is liable to act as narcotic poison.

Pennisetum typhoides Rich. The Bulrush Millet, Spiked Millet; (Hind.—Bájrá; 1am.—Cambu). Largely cultivated as rainy-season crop especially in N. W. F. P., Oudh, Bihar, Bombay and S. India. Used mostly by poor as principal food, supposed to be heating, for this reason consumed mostly in winter in Northern India and Bihar. Unhusked grains contain albuminoids 10.4, starch 71.5, oil 3.3, potash 0.4, and phosphoric acid 0.68 per cent.

Setaria italica Beauv. (Syn.—*Panicum italica* Linn.). The Italian Millet; (Hind.—Kangni; Tam.—Tennai). Generally cultivated although in comparatively small amount in plains and on hills upto 6,500 ft. Largely used in Patna, Saran, Bhagalpur, Dinajpur, and Purniah. Generally regarded nutritious and digestible, in some places considered rather heating. Composition as in *P. miliaceum* Linn.

Sorghum vulgare Pers. The Indian or Great Millet, Guinea Corn; (Sans.—Zúrna; Hind. & Beng.—Juár; Tam.—Cholam). Extensively cultivated generally as hot weather, occasionally as cold weather crop. Common food for labouring classes, easily digestible, less wholesome than maize. Contains nitrogenous substance 9 to 10, starch 60 to 70, and fat 4 to 5 per cent.

Triticum vulgare Villars. (Syn.—*T. sativum* Lamk.). The Wheat, (Hind.—Gheén, kanak; Beng.—Gín; Tam.—Godumai). Under this name are grouped all the species and varieties of wheat, numbering 12, according to the classification by Howard and Howard in "*Wheat in India*". They are extensively cultivated in the whole of Northern India up to Gangetic Delta, in Southern India, the whole of tableland above the Ghats, and many other places up to 18,000 ft. in the Himalayas and Tibet. Used in three different forms *súji*, *maida*, and *atta*; staple article of food in provinces where rice is not used; best of all diets used by Indian races if taken as whole wheat flour *atta*. Chemical composition varies a good deal, on average contains nitrogenous substance 11 per cent. or more, starch 53 to 70, and fat 1.65 to 2.08 per cent.; calorific value of flour 1625 (per lb.); has little Vitamin A, moderately rich in B.

Zea Mays Linn. Maize, Indian Corn; (Sans.—Yavanala; Hind.—Bhuttá, makai; Tam.—Makká-sholam). Cultivated in many parts of India; sown in June and July, cut in September. In the Punjab, N. W. F. P., and throughout Benares, Patna, and Bhagalpur Divisions, assumes the position of staple article of food especially for the peasantry. Contains nitrogenous substance 9 to 10, starch 60 to 70, and fat 4 to 5 per cent.; calories 96 per ounce; yellow maize moderately rich in Vitamins A and B. Not considered as wholesome as wheat, thought to be rather heating.

BUCKWHEAT

Fagopyrum esculentum Moench. (Punj.—Kálá trumbá, pháprá; Nep.—Titáphápur). Cultivated in several parts of Northern India, especially in hills, ascending up to 11,500 ft. in Kumaon. Used by poor classes. Contains albumin 14.2, starch 63.6, and oil 3.4 per cent.

(Note.—About 6 species of Buckwheat are grown in India; composition of the fruits does not differ very widely from the millets).

PULSES

The seeds of leguminous plants, generally known as pulse, differ chemically from the cereal grains in several particulars. They contain a higher percentage of protein, rarely yield less than 2½, and often as much as 4 per cent. of mineral matter or ash, and sometimes contain rather more fat—a constituent which may rise to 17 per cent. in soya-beans or even 50 per cent. in pea-nuts—see below and under edible oils. The digestibility of the proteins in pulse, however, has been usually regarded as low as compared to the corresponding compound in cereals. Slow but thorough cooking of the seeds is essential. It is also desirable to wash most kinds of pulse in cold water. A brief soaking in water to which a little carbonate of soda has been added, especially in the case of lentils, has a useful effect; the alkaline liquor removes a part of the bitter principle present in the pulse, and is then thrown away.

Cajanus indicus Spreng. The Pigeon-pea; (Sans.—Adhakī tubarfkā; Hind. & Beng.—Arhar; Tam.—Thovaray). Extensively grown throughout India upto 6,000 ft. in Himalayas; sown in June or July and reaped in December to March. One of the best, easily digestible, sometimes produces costiveness. Contains protein 21.70, carbohydrate 54.06, and fat 2.50 per cent.

Cicer arietinum Linn. The common Gram or Chick-pea; (Hind.—Chanā, chholā; Beng.—But; Tam.—Kadalai). Extensively cultivated as 'rabi' crop throughout India, especially Northern Provinces and the Nilgiris. Much eaten by the poor; considered antibilious. On an average contains protein 19.91, carbohydrate 54.22, and fat 4.34 per cent.

Dolichos biflorus Linn. Horse Gram or Kooltee; (Hind.—Kālthī; Beng.—Kurti-kalai; Tam.—Kollu). Wild in Himalayas to Ceylon and Burma, ascending, up to 3,000 ft. in Sikkim; sometimes cultivated. Eaten by the poor, continued use said to cause cedematous swellings in some districts. Contains albumin 22.5, starch 56, and fat 1.9 per cent.

D. Lablab Linn. The Lablab-bean; (Hind.—Śm, lobiā; Beng.—Shim; Tam.—Mutchchēh). Wild and cultivated throughout India upto 7,000 ft. in Himalayas. Ripe seeds and green pods both used as vegetable. Composition varies, on an average contains albumin 17.1, starch 57.4, and oil 0.8 to 2.3 per cent.

Glycine Soja Sieb. & Zucc. (Syn.—*Soja hispida* Moench). The Soya bean; (Hind.—Bhat; Beng.—Gari-kulay). Extensively cultivated throughout India and in Eastern Bengal, Khasia Hills, Manipur, the Naga Hills, and Burma generally as 'kharif' crop; often found as weed on fields. Very few vegetable products are so rich as this bean in proteins and in fat or oil; proteins of fairly good quality. Contains nitrogenous substance 35, carbohydrate 26 (in dry substance), and fat 17 per cent.

Lathyrus sativus Linn. The Jarosse or Gesse, The Vetchling; (Hind.—Khesārī; Beng.—Teorā; N. W. F. P.—Churāl). Cultivated all over India, from the Northern indigenous area to Southern, Eastern, and Western Presidencies as cold weather crop. Eaten by the poor; reason to suspect occasional presence, in injurious proportion, of poisonous bitter principle; almost universally regarded in Bengal as unwholesome and deranging digestion. Contains nitrogenous substance 24.9, starch 30, and fat 2.2 per cent.

Lens esculenta Moench. The Lentil; (Hind.—Masūr; Tam.—Misarpurpur). Grows on almost any soil; cultivated in all parts of India especially N. W. Provinces, C. P., and Madras as cold weather crop. Highly nutritious; found useful in treatment of chronic constipation. Contains protein 25.47, carbohydrate 55.03, and fat 3 per cent.

Phaseolus aconitifolius Jacq. The Aconite-leaved Kidney Bean; (Hind.—Moth; Beng.—Banmudgā kheri; Tam.—Tulka-pyre). Found

throughout India upto 4,000 ft. in North-West. Cultivated specially in U. P., Bihar, Purniah District, and Assam generally as 'kharif' crop. Contains albumin 23.8, starch 56.6, and fat 0.6 per cent.

Phaseolus lunatus Linn. The Lima or Duffin Bean; (Hind.—Kursum-bulle-pullie; Beng.—Bunbur-butti; Punj.—Lobíyá). Resembles French bean and frequently referred as such. Cultivated almost everywhere. Seeds much esteemed as 'dal'. Contains nitrogenous substance 17.3 to 18.9, starch 58 to 63, and fat 0.5 to 1.3 per cent.

P. Mungo Linn. The Green Gram; (Hind.—Múṅg). Universally cultivated upto 6,000 ft., also wild. Highly esteemed, resorted to in sickness. Contains protein 23.62, carbohydrate 53.45, and fat 2.69 per cent.

P. radiatus Linn. (Hind.—Urad; Beng.—Mash-kalsi; Punj.—Másh, máli; Tam.—Patchay-pyre). Most esteemed of all pulses. Contains protein 22.38, carbohydrate 55.22, and fat 1.95 per cent.

P. trilobus Ait. The Three-lobed Kidney Bean; (Hind & Beng.—Mugáni; Tam.—Pani-pyre). Distributed throughout India, wild and cultivated from 7,000 ft. in Himalayas to Ceylon and Burma. Highly nutritious, much esteemed by certain classes, eaten by the poor only.

P. vulgaris Linn. The Kidney, French, or Haricot Bean (Hind.—Bakla; Punj.—Bábrí; Tel.—Bari galá). Universally cultivated in tropical, sub-tropical, and temperate regions, nowhere known in wild state. Unripe pods used as green vegetable, ripe seeds often unwholesome but highly nutritious. Contains nitrogenous substance 16 to 25, starch 53 to 63, and fat 1.75 per cent.

Pisum sativum Linn. The Garden Pea; (Hind.—Matar; Beng.—Burra mattar; Tam.—Pattanie). A familiar garden herb; cultivated all over India as 'rabi' crop. Green pods largely eaten before general crop is cut. Contains nitrogenous substance 23.35, starch upto 50, and fat 1.88 per cent.

Vigna Catjang Endl. The Chowbe of India, Tow Cok of China, Catjang Beans; (Hind.—Lobí; Beng.—Barbati; Punj.—Rawán; Tam.—Caramunny-pyre). Commonly cultivated as 'kharif' crop; white seeded form generally considered best. Thought to be rather heating and less digestible than 'urad' or 'múṅg'. Contains albumin 24, starch 57, and fat 1.3 to 3 per cent.

Principal Edible Oils of India

VEGETABLE OILS

Aleurites triloba Forst. (Syn.—*A. moluccana* Willd.). The Belgaum or Indian Walnut, the Candle-Nut; (Sans.—Akshota; Hind.—Akhot; Tam.—Náttu-akrotu-kottai). Cultivated or wild in many parts of S. India, N. W. F. P., and the Punjab, etc. Nuts yield 50 per cent. amber coloured, very fluid, odourless Nut oil or Artist's oil called 'kekuna' in S. India.

Amacardium occidentale Linn. The Cashew-nut; (Hind. & Bomb.—Kájá; Beng.—Hijli bádám; Tam.—Mundiri). Found in coast forests of India, Chittagong, Tenasserim, Andaman Islands, and S. India. Kernels yield about 40 per cent. light yellow, bland oil, very nutritious as food; finest quality equal to almond oil, considered superior to olive oil.

Arachis hypogea Linn. The Ground Nut, Earth Nut, or Pea Nut; (Sans.—Buchanaka; Hind.—Múṅghali; Beng.—Chiner-bádám; Bomb.—Bháí-chane; Tam.—Nilak-kadalai). Generally cultivated throughout India, chiefly S. India and Bombay, certain parts of Bengal, more rarely Upper India; grows best on dry, sandy soil. Seeds yield 37 to 50 per cent. clear, straw coloured oil, resembling olive oil in taste; contains

252 calories per ounce, very little Vitamins A and D. Substitute for olive oil.

Bassia butyracea Roxb. The Indian Butter Tree ; (Hind.—Phalwára; Nep.—Chárf). Sub-Himalayan tree from Kumaon to Bhutan between 1,000 to 5,000 ft. Seeds yield a concrete, of hog's lard consistency, inodorous, delicate white coloured oil called 'phulwa' containing 34 parts fluid oil and 6 parts vegetable matter. 'Ghee' adulterant.

B. latifolia Roxb. The Butter or Mahuá Tree ; (Sans.—Madhuka ; Hind. & Beng.—Mahuá, mahwá ; Tam.—Káttu-irrupai). Extending from Kangra, Kumaon, and Oudh, through the Central Provinces and Chota Nagpur to the Western Ghats ; plentiful in Gujrat, C. P., and Bombay Presidency. Kernels yield thick, concrete, greenish yellow oil eaten by Gonds and other Central India tribes. Very inexpensive substitute and adulterant for 'ghee'.

B. longifolia Linn. The Mowa or Mahuá Tree of S. India ; (Sans.—Madhúka ; Hind.—Mohuá ; Beng.—Mohuvá ; Bomb.—Mahwá ; Tam.—Illupi). Large evergreen tree of S. India and Ceylon ; common in Kanara, Mysore, Malabar, the Anamallays and the Circars. Seeds yield yellow, semi-solid oil which becomes rapidly rancid in plains. 'Ghee' adulterant.

Brassica campestris Linn. To this species belong the turnip, the rape, coleseed, colza, and other forms known in Europe. The Indian forms are :—

Var. 1. **dichotoma**, sp. Roxb. (Bazar name.—Káli sarsón). Small, dark or light brown, smooth or minutely rugose seeds yield colza oil.

Var. 2. **glauca**, sp. Roxb. Rape-seed ; (Bazar name.—Rárá-sarsón). About 30 per cent. oil is obtained from this white or light yellow, occasionally deep coloured, smooth seeded variety. Largely used in diet, pickles, preserves, curries, and for other culinary purposes.

Var. 3. **Torla** Duthie & Fuller. Resembles somewhat the summer rape of Germany, the *navette d'été* of France ; (Hind.—Tóriyá). Abundantly grown in districts bordering on the Himalayan Terai.

B. juncea H. f. & T. The Rái or Indian Mustard ; (Hind.—Rái ; Beng.—Rái sarishá). Abundantly cultivated. Seeds yield 20 to 25 per cent. oil ; much purer than that from *B. campestris*, without peculiar rancid smell of rape, clearer in colour.

B. nigra Koch. The Black or True Mustard ; (Hind.—Rái, kálí rái ; Beng.—Rái sarishá ; Tam.—Kadagho). Cultivated in various parts of India and Tibet, chiefly on hills. Seeds yield about 23 per cent. of bland, inodorous oil. Substitute for lard or 'ghee' ; extensively used in cooking.

Buchananla latifolia Roxb. (Sans., Hind., & Beng.—Piyál ; Tam.—Mowda). Found in hot, drier parts of India, from Kumaon ascending to 1,500 ft., and Oudh, through Central India and to Western Peninsula, Burma and Tenasserim. Kernels yield 50 per cent. pale, straw-coloured, limpid, sweet and wholesome oil called 'chironji.' Substitute for almond oil in medicinal preparations and confectionary.

Carthamus tinctorius Linn. The Safflower, Wild or Bastard Saffron ; (Hind. & Beng.—Kusum ; Sans. & Tam.—Kushumbha). Cultivated as dye-plant all over India. Both kinds of fruits—one the cultivated, white and glossy, the other 'karar' smaller, similar shaped, mottled or dusted, brown grey, and white—yield very clear, yellow oil ; 40 seeds of fruit yielding $3\frac{1}{2}$ seeds of oil. Used for culinary purposes.

Cocos nucifera Linn. The Cocoa-nut Palm ; (Sans.—Nárikela ; Hind.—Náriyal ; Tam.—Tenna). Cultivated in hot damp regions of India, Burma, and Ceylon, especially near sea ; with several cultivated

varieties. Sliced kernel, dried at ordinary temperature yields 80 to 50 per cent. pale yellow, nearly as fluid and limpid as water in tropical climate, of the consistency of lard in temperate climate and of fine white colour, sweet oil liable to become rancid in short time; contains 252 calories per ounce, little Vitamin A and very little D.

Cucumis Melo Linn. The Sweet Melon; (Sans.—Kharvujá; Hind. & Bomb.—Kharbujá; Tam.—Vellari-verai). Extensively cultivated for its fruit in sandy basins of rivers. Seeds yield sweet edible oil. Fruit chiefly eaten as such and not allowed to ripen, hence supply of melon oil not extensive.

Eruca sativa Lamk. (Sans.—Siddhartha; Hind.—Táramítrá; Beng.—Shwet-sarsha). Closely allied to mustards; extensively cultivated as cold weather crop in Northern and Central India, ascending upto 10,000 ft. in Western Himalayas. Oil from seeds used to certain extent as food, sometimes employed in preparation of sweet-meats.

Garcinia Morella Desr. The Gamboge Tree; (Sans., Hind., & Beng.—Tamal; Tam.—oil=Makki). Found in forests of Eastern Bengal, the Khasia Mountains, the Western Peninsula (Malabar and Kanara), and Ceylon. Semi-solid, yellow fat procurable in moderate quantities from seeds. Used as substitute for 'ghee' by the poor.

Gossypium herbaceum Linn. The Cotton Plant; (Sans.—Karpas; Hind., Beng., & Bomb.—Kapás=the floss; Tam.—Parutti). Under this name are grouped series of forms for convenience sake, cultivated. Seeds yield faint yellow cotton-seed oil, liquid at ordinary temperature, with distinctly higher refractive index than that of lard. Substitute for linseed oil which it resembles in taste and odour, contains 252 calories per ounce, very little Vitamin A. Suitable for culinary purposes when purified.

Guizotia abyssinica Cass. Niger Oil; (Hind.—Kálá-til; Beng.—Rámtil; Tel.—Valesulá). Extensively cultivated in various parts of India. Shining black achenes yield 35 per cent. clear, limpid, pale, sweet oil; largely employed for culinary; chief substitute for 'ghee' among poor; extensively used to adulterate gingelly and castor oil.

Helianthus annuus Linn. The Sunflower; (Sans. & Beng.—Suria-mukhi; Hind.—Súrajmukhi; Tel.—Aditya bhakti-chettu). Largely cultivated in China and Tartary, also in Russia, Germany, Italy, and France; to a small extent in India, chiefly in gardens. Oil from seeds, when pure, said to be equal to olive or almond oil for culinary and table purposes and used for adulterating these.

Impatiens Balsamina Linn. The Garden Balsam; (Hind.—Gul-mendi; Punj.—Bantil; Beng.—Dupati; Bomb.—Terada). Plentiful in the North-West Himalayas about 3,000 ft.; cultivated in gardens. Seeds yield edible oil.

I. racemosa DC. Common in Temperate Himalayas; from Simla, 5,000 to 7,000 ft., to Sikkim, 6,000 to 12,000 ft. Seeds yield edible oil.

I. Royel Walp. Common in Temperate Western Himalayas from Nepal to Marri, 6,000 to 8,000 ft. Oil from seed edible.

I. sulcata Wall. Frequent in Temperate Himalayas, 7,000 to 12,000 ft. Seeds yield edible oil.

Juglans regia Linn. The Walnut Tree; (Sans.—Akshota; Hind. & Beng.—Akhrot; Kash.—Dún; Tam.—Akrottu). Found wild and cultivated in Temperate Himalayas and Western Tibet, from Kashmir and Nubra eastwards from 3,000 to 10,000 ft., also in Manipur and Ava Hills. Albuminous kernels afford about 50 per cent. clear, sweet oil; first oil which escapes on expression termed 'virgin' and reserved for feeding purposes; almost colourless, with feeble odour, not disagreeable flavour; Sp. Gr. 0.928 at 16°C, thickens to butter-like consistence at 15°C, solidi-

fies to white mass at 27½°C. Largely used as substitute for olive oil in some European countries, but not considered as first class alimentary oil.

Linum strictum Linn. (Punj.—Basant, babsant). Found on the Punjab hills extending to Peshawar and Marri and in Tibet; grown in Afghanistan on account of oil-yielding seed. Oil very probably does not differ essentially from ordinary linseed oil.

L. usitatissimum Linn. Linseed; (Sans.—Atasi; Hind.—Alsí; Beng.—Tísi; Bomb.—Alási; Tam.—Al-shi-virai). Cultivated chiefly for oil throughout plains of India upto 6,000 ft. Seeds nearly always adulterated, especially with rape; yield of oil varies, weight for weight, white seed is said to give more oil and has thinner cuticle than red; 30 to 35 per cent. of oil obtainable from seed; contains 252 calories per ounce, very little Vitamin A. Linseed oil is very little used in India as food; in country about Nagpur used as an article of diet and the purgative properties not perceptible.

Olea europæa Linn. The Olive. Attempts made to cultivate in various parts of India but with little success except in Kashmir near Garhi. Tree flowers but fruits seldom set. Oil much consumed as article of food by Europeans; contains 250 calories per ounce, very little Vitamin A.

Papaver somniferum Linn. The Opium or White Poppy; (Sans.—Alhiphena; Hind., Beng., & Bomb.—Afsm; Tam.—Posta-Katol). Cultivated throughout the country especially in Native States. Permission to cultivate in India governed by regulation regarding opium. Poppy seed-oil yield dependant on freshness of the seed; 35 per cent. obtainable; readily bleaches on exposure to the sun and becomes transparent and almost tasteless, has no intoxicating properties;

Perilla ocimoides Linn. (Hind.—Bhanjirá; Naga.—Kenia; Kumaon.—Bhangará). Common in Tropical and Temperate Himalayas; from Kashmir to Bhutan at 1,000 to 10,000 ft., also Khasia mountains 3,000 to 6,000 ft., often cultivated on Himalayas 4,000 to 5,000 ft. for small aromatic seeds. Aromatic oil used by hill-men of North-West Himalayas and Manipur for culinary purposes

Pistacia Terebinthus Linn., var. *mutica* Aitch. et Hemsley. The Terebinth Tree; (Hind. & Bomb.—Kábuli mustakí; Punj.—Khinjak; Baluch.—Ban, wan, gwan). Commonly grown in Baluchistan. Kernels yield mixture of essential and fatty oil which is eaten as a relish with 'karut' (dried oxygal) and bread.

P. vera Linn. The Pistachio Nut; (Hind., Beng., & Bomb.—Pistá). Forming forests at 3,000 ft. upwards, usually on sand stone formations in Syria, Damascus, Mesopotamia, Terek, Orfa, and Khorasan; extensively cultivated in Syria, Palestine, and Persia; a few trees cultivated here and there in the North-West India. Nuts contain 60 per cent. fatty, greenish, sweet-flavoured aromatic oil; occasionally used as food, but rapidly becomes rancid.

Prinsepia utilis Royle. (Hind.—Bhekal; Punj.—Gurindá, rárf). On dry rocky hills of Temperate Himalayas, from Hazara to Sikkim and Bhutan, 3,000 to 9,000 ft., also on Khasia Hills. Seeds yield an oil much used in North-West Himalayas for food.

Prunus Armeniaca Linn. The Apricot, Mishmus, or "Moon of the thful"; (Hind.—Khubáni, zardálá; Punj.—Hárf). Commonly cultivated between Indus and Sarda, in North-West Himalayas, the Punjab plains, and in Afghanistan; fruit ripens well up to 10,000 ft., but best between 6,000 and 9,000 ft.; very frequently spontaneous. Seeds yield clear oil, of pale yellow colour, contains hydrocyanic acid, has pleasant flavour with odour of bitter almonds. Extensively used in North-West Himalayas, especially Kashmir, for cooking.

Prunus Persica Benth. & Hook. *f.* The Peach and Nectarine; (Hind. & Panj.—Ará). Widely spread all over North-West Himalayas and occurs near almost every village upto 10,000 ft., S. India, Ceylon, and Burma. Oil from kernels resembles that of bitter almonds; substitute for the same. Used in the North-West Himalayas and Kashmir for cookery.

Sesamum indicum DC. Gingelly or Sesame oil; (Sans.—Tila; Hind., Beng., & Bomb.—Til; Tam.—Yellu-cheddie). Commonly grown as autumn or even winter crop throughout warmer parts of India and as summer one in colder almost exclusively for oil-yielding seeds. Black seed form 'Kálá til' more common and yields superior oil than white form 'Safed til'. Gingelly oil clear limpid, colour varies pale yellow to dark amber, odourless, not liable to become rancid; frequently adulterated with ground-nut oil, resembles olive oil in many properties, contains 252 calories per ounce, very little Vitamin A. Used for human consumption, sweet-meat making and for adulterating the oil of almonds and 'ghee.'

Theobroma Cacao Linn Cultivated in Southern Presidency and Ceylon. Light yellowish, opaque, solid oil called 'Cacao butter' obtained by pressing warmed seeds; these when shelled yield 45 to 50 per cent. oil. Cacao butter dry at ordinary temperatures, unctuous to touch, but brittle enough to break into fragments when struck exhibiting dull waxy fracture, has pleasant odour of chocolate, melts in mouth with bland, agreeable taste; Sp. Gr. 0.961, fuses between 20° to 30°C, does not become rancid from exposure.

Viburnum coriaceum Blume. (Nep.—Bará gorakuri; Kumaon.—Kálá titaliyá). Common on Himalayas from the Punjab to Bhutan at 4,000 to 8,000 ft., also found in Khasia Hills, the Nilgiris, and Ceylon. Nepalese use the oil from seed.

ANIMAL FATS AND OILS

Beef marrow. Large hollow bones of ox contain fat (marrow) which is identical with tallow, with characteristic taste due to cellular tissue which accompanies it; reddish, hard, tallowy, exhibits granular structure when set after melting, consists of 70 per cent. palmitin and stearin, 30 per cent. olein, becomes rancid sooner than tallow, melting point 45°C. Used for alimental purposes, as an addition to soups.

Beef tallow. Prepared from fat of ruminating animals (oxen, cows, steers, and calves) by melting crude tallow and pressing residual cellular tissue, particles of flesh, etc. It is hard and solid, pale yellow or white, tasteless, inodorous in fresh state, assuming after short time rather unpleasant characteristic smell without becoming rancid. Consists almost entirely of palmitin, stearin, and olein, proportions of which vary according to the parts of animal whence tallow is derived; softest and richest in olein from scrotum, hardest and richest in stearin from intestines; iodine number (thermal) 40°C., contains 0.34 gm. of protein per oz. Used as food-stuff for cooking and frying, in a special form as substitute for butter.

Butter. Prepared mostly from cow's and buffalo's milk by continuous and strong agitation; buffalo's milk richer in fat; composition varies considerably, 85 per cent. fat to 86 per cent. water. Because of water and casein butter turns quickly rancid, which is avoided by kneading it with 8 to 4 per cent. of common salt after thorough washing, better by keeping it in melted condition until thoroughly clarified and then separating it from precipitated water and casein. Apart from traces of colouring matter, lecithin, cholesterolin, etc., pure butter consists solely

of tri-glycerides of fatty acids; colour varies from very pale to fine deep yellow. Melting point of cow's butter 31° to 31.5°C. , iodine number generally 28.0 to 35.1, rich in Vitamin A, contains little of D, calories per lb. about 3,500. Generally, however, in India it is carefully remelted by itself on fire when a froth, mainly consisting of unremoved casein, collects on the surface of the liquid which is removed and used as 'Ghec'.

Butter (artificial), oleomargarine, etc. Prepared from constituents of beef tallow by special processes and worked up with milk and vegetable oils. Greatly resembles, even identical with natural butter in appearance, consistency and flavour.

Goose fat. From accumulations of fat interspersed among tissues and under the skin of goose by carefully melting cut-up fat and straining to separate the product from cellular tissue. White to pale yellow, translucent, granular, frequently almost liquid at 10° to 12°C. , of agreeable flavour, does not easily turn rancid, melting point 25° to 26°C. , iodine number 71.5.

Hare fat. White, occasionally somewhat yellowish, with characteristic smell and mild agreeable taste, consistency rather softer than that of lard; melting point 44° to 46°C. ; solid, insoluble fatty acids 95.47 per cent.

Hog's lard. From fatty portions of hog, especially those lying beneath the skin and between intestines; that from the exterior fatty integument surrounding entire carcase immediately below the skin (especially on back and sides) is more solid and curdy, more easily melted out than from interior of the body. Fat more consistent during January and February than during warmer seasons and richer in stearin, summer fat contains more olein; best quantity and quality in consistency and appearance supplied by intestinal fat of young pigs. Hog's lard is white, granular, of salvy or pappy consistency; with agreeable, rather sweet, fatty taste; turns rancid quickly on exposure to air, consists of olein, palmitin, stearin, and 0.23 per cent. of unsaponified matter, iodine number 59.0, contains very little of Vitamin A. Prepared like tallow. Used for alimental purposes as edible fat and for cooking and frying.

Lard oil. Obtained by pressing hog's lard at 0°C. leaving behind tallow. Thinly fluid like olive oil, pale yellow.

Mutton tallow. Prepared from accumulation of fat in flesh and tissues of sheep like beef tallow. Similar to that of ox but less highly coloured, white, rather hard, brittle, initially inodorous, assumes characteristic smell and taste of mutton after brief exposure to air, becomes rancid very quickly when smells like goat's fat; Sp. Gr. 0.860 at 100°C. , consists of about 70 per cent. stearin and palmitin (margarine) and 30 per cent. of olein. Uses similar to those of beef tallow.

Principal Indian Oils and Fats used in Medicine

Albizia Lebbek Benth. The Siris Tree. In leprosy.

Aleurites triloba Forst. (Syn.—*A. moluccana* Willd.). The Belgaum or Indian Walnut. Mild purgative, dressing for ulcers, castor oil substitute.

Allium Cepa Linn. The Onion. Expectorant, diuretic, stimulant.

A. sativum Linn. The Garlic. Stimulant, rubefacient, used externally in paralytic and rheumatic affections.

Anomum subulatum Roxb. Aromatic stimulant.

Anacardium occidentale Linn. The Cashew-nut. Irritant, rubefacient, vesicant, externally used in leprosy.

Aquilaria Agallocha Roxb. The Eagle-Wood. Internally in fever, externally in colic.

Arachis hypogæa Linn. The Ground Nut. Substitute for olive or salad oil.

Argemone mexicana Linn. The Mexican or Prickly Poppy. In ulcers and eruptions.

Atalantia monopylla Coll. The Wild Lime. In chronic rheumatism.

Bassia butyracea Roxb. The Indian Butter Plant. In rheumatism and contraction of the limbs.

B. latifolia Roxb. The Butter or Mahua Tree. In cephalalgia and skin diseases.

B. longifolia Linn. The Mahua of S. India. Detergent, in skin diseases.

Beef tallow. For ointments.

Benincasa cerifera Savi. The White Gourd Melon. Anthelmintic.

Brassica campestris Linn. Embrocation, skin preservative.

Buchanania latifolia Roxb. Almond oil substitute.

Butter. Emollient, cooling, stomachic, and variety of purposes.

Cæsalpinia Bonducella Fleming. Fever-nut. Anthelmintic, useful in convulsions and palsy.

Calendula officinalis Linn. Marigold.

Calophyllum Inophyllum Linn. The Alexanderian Laurel. External use in rheumatism.

C. Wightianum Wall. In leprosy, cutaneous affections, scabies, rheumatism.

Carthamus tinctorius Linn. The Safflower. In rheumatic pains, paralytic affections, ulcers.

Cedrus Libani Barrel, var. *Deodara* Loud. The Deodar, Himalayan Cedar. In inflated skin, ulcers, eruptions, sore feet in cattle, leprosy, skin diseases.

Celastrus paniculatus Willd. The Black Oil. In rheumatic pain, fistulæ, sinuses, beri-beri; diaphoretic, diuretic, nervine tonic.

Cocos nucifera Linn. The Cocoa-nut Palm. In burns, baldness, that from shell in ringworm.

Croton oblongifolius Roxb. Purgative.

C. Tiglium Linn. The Purging Croton. Drastic purgative, powerful hydragogue, cathartic, counter irritant; in dropsy, apoplexy, paralysis.

Cuminum Cyminum Linn. The Cumin. Stimulant.

Cynometra ramiflora Linn. In leprosy and other cutaneous diseases.

Dalbergia lanceolaria Linn. In rheumatism.

D. Sissoo Roxb. The Sissoo. Wood yields empyreumatic medicinal oil.

Dipterocarpus a'tatus Roxb. The Gurjun oil. In leprosy.

D. tuberculatus Roxb. The Eng Tree. In leprosy, ulcers.

D. turbinatus Gært. f. (Syn.—*D. laevis* Ham.). The Gurjun or Kanyin Oil. Externally and internally in leprosy, ringworm, gonorrhœa, mucous discharges.

Dugong oil. Oil of the Sea Hog, the Yungan or Mooda Hoor. Substitute for cod-liver oil.

Gossypium herbaceum Linn. The Cotton Plant. Liniment in rheumatic affections.

Gulrotia abyssinica Cass. Niger Oil. See Sesamum Oil.

Gynocardia odorata R. Br. The Chaulmoogra. In rheumatism, phthisis, leprosy, psoriasis, skin diseases, etc.,

Helarrhena antidysenterica Wall. The Kyrchi.

Hydnocarpus venenata Gært. In Cutaneous diseases, leprosy, substitute for chaulmoogra oil.

- Hydnocarpus Wightiana** Bl. In ulcers; substitute for chaulmoogra.
- Jatropha Curcas** Linn. Purgative, also external application.
- Lard** (fat of the pig). In inflammation, bruises, sprains, eruptions, eczema, erysipelas, etc.
- Linum usitatissimum** Linn. The Linseed. Aperient, in the preparation of liniment for burns, external application.
- Mallotus philippinensis** Muell. The Monkey Face Tree. Cathartic.
- Melaleuca Leucadendron** Linn. The Cajput. Stimulant, diaphoretic.
- Melia Azadirachta** Linn. The Neem or Margosa Tree. Anthelmintic, antiseptic; externally to ulcers, in rheumatism, headache, skin diseases.
- Mesua ferrea** Linn. Externally for sores, embrocation in rheumatism.
- Moringa pterygosperma** Gærtn. The Horse Radish Tree. In gout and acute rheumatism.
- Myristica malabarica** Lamk. Stimulating application in indolent ulcers, detergent, anti-rheumatic.
- Nerium odorum** Soland. Sweet-scented Oleander. In cutaneous diseases and leprosy.
- Olea europæa** Linn. The Olive. Emollient, nutrient, mild laxative, demulcent.
- Papaver somniferum** Linn. The Opium or White Poppy. Demulcent, substitute for linseed oil.
- Petroleum**. Embrocation.
- Pistacia vera** Linn. The Pistachio Nut. Demulcent, restorative.
- Pongamia glabra** Vent. In skin diseases, rheumatism, leprosy.
- Prinsepia utilis** Royle. Rubefacient, in rheumatism and pain due to fatigue.
- Ricinus communis** Linn. The Castor Oil Plant. Mild demulcent, laxative.
- Sarcostigma Kleinii** W. & A. In rheumatism.
- Schleichera trijuga** Willd. The Lac Tree. To scalp for hair growth, original Macassar oil.
- Semecarpus Anacardium** Linn. f. The Marking Nut Tree. In rheumatism and leprosy.
- Sesamum indicum** DC. The Gingelly or Sesame Oil. Demulcent, in piles and dysentery.
- Strychnos Nux-vomica** Linn. The Nux-vomica or Strychnine Tree. External application in chronic rheumatism.
- Taraktogenos** Kurzii King. The Chaulmoogra. In leprosy and many skin diseases.
- Vernonia anthelmintica** Willd. The Purple Flea-Bane.
- Xanthium Strumarium** Linn. Bur-weed.

Principal Edible and Poisonous Fungi of India

Contrary to the general belief, the number of kinds of fungi that are really poisonous is comparatively few. There are several species of fungi eaten indiscriminately in India and, indeed, if properly cooked, few are dangerously poisonous. If macerated in vinegar before being cooked, and if eaten with plenty of bread, there is almost no danger. Cases of fungus poisoning, however, are not unheard of in India, but the subject is, at present, very imperfectly known and the literature hardly throws any light whatsoever. The safest proceeding, therefore, is to learn to recognise the good species, and never to eat a fungus until its identity is certain. Researches of Dupetit indicate that all edible mushrooms contain a poisonous principle, which is destroyed at a temperature of 100°C. and mushrooms rendered innocuous.

Although strict botanical determination cannot be too strongly emphasised, yet a few characters by which a wholesome mushroom may be recognised are :—(i) They are found growing in fields or in open grassy places in forests (ii) They are scattered, each rising direct from the ground (iii) The stem should break easily when touched, it should spring from the centre of the pileus The cap should be thick relatively to the gills. (iv) They should not be acid in flavour nor smell. (v) The bright rosy or pink gills and the absence of any yellow stain when bruised are two good tests. It does not, however, follow that fungi, not answering to the above, are all poisonous; indeed, *Hydnum repandum* and *Cantharellus cibarius* are both acid, yet are excellent articles of food.

The available nutrient material of edible fungi is very small, their chief value is as a flavouring agent or condiment giving palatability to the plainer but more nutritious foods, and adding welcome variety to meals

EDIBLE FUNGI

Besides the following, there are, no doubt, many other forms widely used as food in India but, owing to the meagreness of the literature on the subject, complete list cannot be given.

Agaricus campestris Linn. The Mushroom; (Sans.—Chattrak; Kash.—Mánskhel, Beng.—Banger chhátá; Sant.—Ot; Bomb.—Alombe) Generally in damp *debris* throughout India during rainy season; universally eaten fresh or dried.

A. mitto Pers Kurrum

A. ostreatus Jacq. (Cutch & Bomb.—Phanasa-alambe, or vulgarly phansamba). Grows upon stumps of old jack-trees (phanas).

Cantharellus cibarius Fr Kashmir, Peshawar, Mussoorie.

Collybia albuminosa (Berk) Betch (Syn.—*Leptota albuminosa* Berk).—(Beng.—Durga-chhátá). Bengal, C. P., and Berar. Grows from inside the termites' nests; eaten with relish.

Coprinus comatus (Battara) Fr. The Mushroom; (Hind & Punj—Khumbi, khumb). Punjab, United Provinces, and several other parts of India. Eaten fresh or dried. Collected during rainy season.

Entoloma microcarpum Berk & Broome. (Beng.—Wee-chhátá). Bengal. Grows on the surface of outer crusto of termites' nests; commonly eaten by villagers.

Fistulina hepatica Fr. Darjeeling.

Helvella crispa Fr. Common in Afghanistan.

Hirneola polytricha Mont. (Syn.—*Exidea polytricha* Mont.). Belgaum, Poona, Dharwar, Nidungayam, Malabar, and Burma.

Hydnum caralloides Scop. Darjeeling 7,500 ft., Chitral, N. W. F. P. (common) and Afghanistan. In crevices of old tree-trunks; collected during August; dried in the sun and largely used.

H. repandum Linn. Mussoorie, United Provinces.

Lactarius deliciosus Fr. Sikkim.

Lentinus subnudus Berk. Common in Bengal, Kadala, and Bombay. On dead branches of logs. Eaten by Kholes fresh and young.

Leptota mastoidea Fr. Bengal.

L. procera (Scop.) Sacc. Saharanpur.

Lycoperdon sp. Puff-balls, Bengal, Kashmir and many parts of Western Himalayas.

Melanogaster durissimus Cooke. Truffle. Simla (abundant), Kangra. Occasionally eaten.

Morchella esculenta Pers. The Morell; (Punj.—Guchhíán—plains, káná kach—hills). Fleshy fungus abundant in Kashmir, Chanba and many parts of Northern Punjab.

Pleurotus cretaceus Massee. (Vern.—Dhingri). Peshawar and C. P. On wood.

P. fimbriatus Rolt. C. P. and Berar.

Polyporus squamosus (Huds) Fr. Darjeeling, 7,500 ft.; Pangi, N. W. Himalayas. On dead wood.

Truffles. Stewart describes some being found in Kashmir. Badhwar has recently collected some blackish-brown ones from the Kagan valley, locally known as 'usri'. They are highly flavoured and their presence in the soil is discovered by the villagers by smell in September-October when they are said to develop the flavour best. Goats are also said to dig out some during grazing and eat. (Also see *Melanogaster durissimus* above).

Vo'varia diplasia Berk & Broome. (Beng.—Pawal-chhátá). Bengal, Burma.

V. terrestria Berk & Broome. (Beng.—Poal-chhátá). Bengal. Grows on heaps of waste paddy straw.

(In addition Stewart mentions another species as being freely eaten in the Punjab, which is known as 'shíríán' in the Jhelum and 'bat-bakri' in the Kair valley. It is a thin, flat, ragged-looking fungus, yellow above and with white gills below, which is found on dead trees in various parts of the Punjab Himalayas at 8,000 to 8,500 ft. He also mentions an 'underground mushroom' of doubtful species found near Multan, called 'boinphal').

POISONOUS FUNGI

Very little information is available on the Indian poisonous fungi. From time to time cases of fungus poisoning are reported but, it is to be regretted, no further attention has been paid. *Stropharia semiglobata* (Batsch) Quel. from Khasia Hills, *Hypholoma fasciculare* (Huds) Fr. from Darjeeling and Simla, and *Lactarius vellereus* Fr. from Sikkim, are regarded as poisonous. There is also evidence on record that there exists in Bengal a fungus which closely resembles an edible form but which contains *amanitine* or *muscarine*, the poisonous principle of *Amanita muscaria*, by eating which symptoms closely resembling those of intoxication rapidly ensue. Furthermore, *mucor* has been regarded as harmful in India since ages, and the pickles and all edible stuff attacked by it are not thought fit for eating. There are, however, some foreign fungi which are definitely reported to be poisonous. *Amanita phalloides*—the death cap—is responsible for perhaps 90 per cent. of the deaths caused by fungus poisoning in Europe, England, and U. S. A. It is the most dangerous fungus known and very small quantities will cause intense suffering and often death. There are, indeed, several other species of the genus that are very poisonous, e.g., *Amanita muscaria*—fly agaric—and *A. pantheriana*—warted agaric, etc. *Leptota cristata*—crested agaric—and several other small species of *Leptota* are regarded with suspicion and should be avoided. *Volvaria gloiocephala*—glutinous agaric—and its allies have always been regarded as poisonous, but there is recent evidence that they may be eaten without ill effects. *Psalliota xanthoderma*—yellow staining mushroom—has caused illness in some cases,

Parasites of Meat, Fish and Edible Crustacea
MEAT

	Name of parasite	Size	Producing in man	Whether condemned for food
Beef	(a) <i>Cysticercus bovis</i>	6 mm	<i>Taenia saginata</i>	Condemned
	(b) <i>Sarcocystis miescheriana</i>	30 mm × 5 mm (Egypt, Ceylon and India), 2 mm in Europe	Nothing	Not condemned
	(c) <i>Onchocerca gibsoni</i> , adults and larvae contained in nodules	Size of a marble	Nothing	Condemned for its bad appearance
Pork	(a) <i>Cysticercus cellulosæ</i>	6 mm	<i>Tænia solium</i>	Condemned
	(b) Larval <i>Trichinella spiralis</i>	About 600 µ	Adult <i>Trichinella spiralis</i> , giving rise to larval forms in the muscle	Condemned
	(c) <i>Sarcocystis miescheriana</i>	1 mm in Europe	Nothing	Not condemned
Mutton	<i>Sarcocystis miescheriana</i>	1 mm in Europe Cysts often found calcified	Nothing	Not condemned

FISH

	Name of parasite	Size	Producing in man	Whether condemned for food
Fresh-water fishes	Plerocercoids of <i>D. latus</i>	1.5 cm. × 1 mm.	<i>D. latus</i>	Condemned
	Cercariae of <i>Clonorchis sinensis</i>	2 mm	<i>Clonorchis sinensis</i>	Condemned
Marine fishes	Cercariae of <i>Heterophyes heterophyes</i> ?		<i>H. heterophyes</i>	Condemned
	(a) Larval Ascarids	2 cm. × 1 mm.	Nothing	Not condemned
	(b) Adult hair-like nematodes	2 to 3 cm.	Nothing	Not condemned
	(c) Larval cestodes	Globular, about 6 mm.	Nothing	Not condemned

EDIBLE CRUSTACEA

	Name of parasite	Size	Producing in man	Whether condemned for food
Crabs and crayfish	Cercariae of <i>Paragonimus westernanti</i>	About 2 mm.	Adult <i>Paragonimus westernanti</i>	Condemned

(Parasitology, Blacklock and Southwell)

MEAT, FISH AND EDIBLE CRUSTACEA AS A VEHICLE IN THE SPREAD OF DISEASES

Food poisoning	Through ingesting meat or fish. Infected with <i>Bact. enteritidis</i> , <i>Bact. artricke</i> , <i>Bact. paratyphosum</i> B and Hirschfeld's bacillus, <i>Proteus vulgaris</i> , etc.
Botulism	Due to ingestion of fresh and tinned meats and fish infected with <i>Cl. Botulinum</i> .
Tuberculosis	Due to ingested meats infected with <i>Myco. tuberculosis</i> .
Anthrax	Due to ingestion of meat of an animal infected with <i>B. anthracis</i> .
Enteric group of fevers		...	Due to ingesting infected shell fish, oysters, etc.

FOOD OTHER THAN MEAT, FISH, AND EDIBLE CRUSTACEA AS A VEHICLE IN THE SPREAD OF DISEASES

Bacterial :

Food poisoning	Due to infected canned and tinned fruits and vegetables by <i>Bact. enteritidis</i> , etc. <i>Proteus vulgaris</i> . <i>Bact. paratyphosum</i> A, B and C. Detection of the organism is difficult.
Botulism	Due to canned and tinned fruits and vegetables and milk infected with <i>Clostridium botulinum</i> . The appearance of food may be normal. A most powerful exotoxin produced which is heat stable.
Actinomycosis	Due to chewing, infected grain, splinters of straw, etc.
Tuberculosis	Due to ingestion of unboiled or unpasturised milk, from animals, infected with <i>Myco. tuberculosis</i> var. <i>homonis</i> or <i>bovinis</i> . In India most of the cases are direct infections from a case of tuberculosis.

Undulant fever	Due to ingestion of unboiled or unpasturised milk, from goats infected with <i>Br. melitensis</i> and preparations such as butter or cheese prepared from milk. <i>Br. abortus</i> causes similar fever.
Septic throat	Due to ingestion of milk infected with Streptococci. The cow in this case is often a passive carrier of organisms of human origin.
Cholera	Due to ingesting <i>V. cholerae</i> in milk and vegetables infected through carriers or convalescents.
Enteric group of fevers		...	Due to ingesting <i>Bact. typhosum</i> , <i>Bact. paratyphosum</i> , A.B., Hirschfeld's bacillus in milk and vegetables infected through carriers or convalescents.
Diphtheria	Due to ingesting <i>C. diphtheriae</i> infected milk. Rare mode of transmission.
Scarlet fever	Due to ingesting <i>Strep. scarlatinae</i> in milk infected through carriers.
Dysentery	Due to ingesting milk and vegetables infected through carriers of <i>Bact. shigae</i> , <i>Bact. flexner</i> , <i>Bact. sonne</i> , etc.
Summer diarrhoea of infants		...	Do. of <i>Bact. morgani</i> .

Spirochætal:

Spirochætal jaundice	...	Spirochætes in rats' urine, (?) contaminating food.
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Protozoal:

Amœbic dysentery	}	Infective cysts on food.
Balantidial dysentery		

Helminthic:**(a) DUE TO CESTODES:**

Cysticercosis due to larvæ of <i>Tania solium</i>	...	Eggs of <i>Tania solium</i> in food.
<i>Hymenolepis</i> infection	...	Eggs in food.
Hydatid; due to larva of <i>Tania granulosa</i>	...	Eggs of <i>Tania granulosa</i> in food.

(b) DUE TO TREMATODES:

<i>Fasciola</i>	{	infections ...	{	Infective encysted cercariæ on water vegetables.
<i>Fasciolopsis</i>				

(c) DUE TO NEMATODES :

<i>Ascaris</i>	} infections	{ Infective eggs on food, especially vegetables.
<i>Trichuris</i>		
<i>Strongyloides</i>	} infections ...	{ Infective (filariform) larvæ on food, especially vegetables.
<i>Ancylostoma</i>		
<i>Necator</i>		

WATER AS A VEHICLE IN THE SPREAD OF DISEASES

Bacterial :

Enteric group of fevers.	...	Due to drinking of water polluted by—
		1. <i>Bact. typhosum</i> .
		2. <i>Bact. paratyphosum</i> A, B, and C.
		<i>V. cholerae</i> .
Cholera	1. <i>Bact. shiga</i>
Dysentery	2. <i>Bact. flexneri</i> (and flexner group)
		3. <i>Bact. sonnei</i>
		4. <i>Bact. dispar</i> , etc.

Spirochætal :

Spirochætal jaundice	Spirochætes from rats' urine in water.
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Protozoal :

Amœbic dysentery {	}	Infective cysts in water.
Balantidial dysentery {		

Helminthic :

(a) DUE TO CESTODES :

- | | | |
|--|-----|---|
| (1) Cysticercosis due to larvæ of <i>Tænia solium</i> . | ... | Eggs of <i>Tænia solium</i> in water. |
| (2) <i>Hymenolepis</i> infection. | ... | Eggs in water. |
| (3) <i>Sparganosis</i> due to infection with plerocercoids of <i>Dibothriocephalus</i> sp. | ... | (?) Proceroid in <i>Cyclops</i> in water. |
| (4) Hydatid : larvæ of <i>Tænia granulosa</i> . | ... | Eggs of <i>Tænia granulosa</i> in water. |

(b) DUE TO TREMATODES :

- | | | |
|---|-----|--|
| (1) <i>Schistosoma</i> infection (all species). | ... | Infective cercariæ in water. |
| (2) <i>Fasciola</i> infection | } | Infective encysted cercariæ from gass, etc., in water. |
| (3) <i>Fasciolopsis</i> infection | | |

(c) DUE TO NEMATODES :

- | | | |
|---|-----|---|
| (1) <i>Ascaris</i> infection | } | Infective eggs in water. |
| (2) <i>Trichuris</i> infection | | |
| (3) <i>Strongyloides</i> infection | | |
| (4) <i>Ancylostoma</i> infection | } | Infective filariform larvæ in water. |
| (5) <i>Necator</i> infection | | |
| (6) <i>Dracunculus medinensis</i> infection | | |
| ... | ... | Fully-grown infective larvæ in <i>Cyclops</i> in water. |

Posological Table

	IMPERIAL	METRIC
*Acetanilidum (Antifebrinum)	2 to 5 gr.	0·12 to 0·8 gm.
Acidum Acetylsalicylicum ...	5 to 15 gr.	0·8 to 1 gm.
„ Benzoicum ...	5 to 15 gr.	0·8 to 1 gm.
„ Boricum ...	5 to 15 gr.	0·8 to 1 gm.
„ Citricum ...	5 to 80 gr.	0·8 to 2 gm.
„ Hydrobrom. Dil. ...	15 to 60 min.	1 to 4 c.cm.
„ Hydrochlor. Dil. ...	5 to 60 min.	0·8 to 4 c.cm.
„ Hydrocyanic. Dil. ...	2 to 5 min.	0·12 to 0·8 c.cm.
„ Hypophosphorosum Dil. ...	5 to 15 min.	0·8 to 1 c.cm.
* „ Nitricum Dil. ...	5 to 20 min.	0·8 to 1·2 c.cm.
* „ Nitro-hydrochlor. Dil. ...	5 to 20 min.	0·8 to 1·2 c.cm.
„ Oleicum ...	5 to 15 min.	0·8 to 1 c.cm.
„ Phosphoricum Dil. ...	5 to 60 min.	0·8 to 4 c.cm.
„ Salicylicum ...	5 to 10 gr.	0·8 to 0·6 gm.
* „ Sulphuricum Aromat. ...	5 to 20 min.	0·8 to 1·2 c.cm.
„ „ Dil. ...	5 to 60 min.	0·8 to 4 c.cm.
* „ Sulphurosum ...	$\frac{1}{2}$ to 1 dr.	2 to 4 c.cm.
„ Tannicum ...	5 to 10 gr.	0·8 to 0·6 gm.
„ Tartaricum ...	5 to 80 gr.	0·8 to 2 gm.
*Aconitina ...	1/640 to 1/400 gr.	0·0001 to 0·00015 gm.
Adrenalina ...	1/600 to 1/120 gr.	0·0001 to 0·0005 gm.
Agar ...	60 to 240 gr.	4 to 16 gm.
Æther Anæstheticus ...	15 to 60 min.	1 to 4 c.cm.
Aloe ...	2 to 5 gr.	0·12 to 0·8 gm.
Aloinum ...	$\frac{1}{4}$ to 1 gr.	0·015 to 0·06 gm.
*Ammonii Benzoas ...	5 to 15 gr.	0·8 to 1 gm.
„ Bicarbonas ...	5 to 10 gr.	0·8 to 0·6 gm.
* „ Bromidum ...	5 to 80 gr.	0·8 to 2 gm.
„ Chloridum ...	5 to 60 gr.	0·8 to 4 gm.
Amyl Nitris (mouth) ...	$\frac{1}{2}$ to 1 min.	0·08 to 0·06 c.cm.
„ (inhaled) ...	2 to 5 min.	0·12 to 0·8 c.cm.
*Antimonii Oxidum ...	1 to 2 gr.	0·06 to 0·12 gm.
*Antimonium Sulphuratum ...	1 to 2 gr.	0·06 to 0·12 gm.
Antimonii et Potassii Tartras ...	1/82 to 1/8 gr.	0·002 to 0·008 gm.
„ „ „ (emetic) ...	$\frac{1}{2}$ to 1 gr.	0·08 to 0·06 gm.
Antipyrinum (Phenazonum) ...	5 to 10 gr.	0·8 to 0·6 gm.
Apomorphinæ Hydrochlorid. ...	1/64 to 1/82 gr.	0·001 to 0·002 gm.
*Aqua Laurocerasi ...	$\frac{1}{2}$ to 2 dr.	2 to 8 c.cm.
Argenti Nitras ..	$\frac{1}{8}$ to $\frac{1}{4}$ gr.	0·008 to 0·016 gm.
Arseni Triiodidum ...	$\frac{1}{16}$ to $\frac{1}{4}$ gr.	0·004 to 0·016 gm.
„ Trioxidum ...	$\frac{1}{60}$ to $\frac{1}{12}$ gr.	0·001 to 0·005 gm.
Asafetida ...	5 to 15 gr.	0·8 to 1 gm.
*Ascaridole ...	12 to 80 min.	0·7 to 1·8 c.cm.
*Aspirin ...	5 to 15 gr.	0·8 to 1 gm.
Atropina ; Atropinæ Sulphas ...	1/240 to 1/60 gr.	0·00025 to 0·001 gm.
Barbitonum ...	5 to 10 gr.	0·8 to 0·6 gm.
*β-Eucainæ Hydrochloridum ...	$\frac{1}{8}$ to $\frac{1}{2}$ gr.	0·008 to 0·08 gm.
* „ Lactas ...	$\frac{1}{8}$ to $\frac{1}{2}$ gr.	0·008 to 0·08 gm.

*These preparations are non-official.

	IMPERIAL.	METRIC
*Benzo-naphthol . . .	5 to 10 gr.	0·8 to 0·6 gm.
*Berberinæ Sulphas . .	1 to 5 gr.	0·06 to 0·3 gm.
Beta-naphthol . . .	5 to 10 gr.	0·3 to 0·6 gm.
Bismuthi Carbonas, vel Salicylas	10 to 30 gr.	0·6 to 2 gm.
* " Subchloridum, vel *Subnitrates	5 to 20 gr.	0·8 to 1·2 gm.
* " Subgallas . . .	10 to 30 gr.	0·6 to 2 gm.
* " Tartras Solubilis . .	2 to 5 gr.	0·12 to 0·3 gm.
Borax . . .	5 to 15 gr.	0·8 to 1 gm.
*Butyl-Chloral Hydras . .	5 to 20 gr.	0·8 to 1·2 gm.
Caffeina . . .	2 to 5 gr.	0·12 to 0·3 gm.
" et Sodii Benzoas . . .	5 to 15 gr.	0·8 to 1 gm.
*Caffeinæ Citras . . .	2 to 10 gr.	0·12 to 0·6 gm.
*Calciferol . . .	—	0·0001 to 0·0005 gm.
Calcii Carbonas . . .	15 to 60 gr.	1 to 4 gm.
" Chloridum . . .	10 to 30 gr.	0·6 to 2 gm.
* " Glycerophosphas . .	8 to 10 gr.	0·2 to 0·6 gm.
* " Hypophosphis . . .	8 to 10 gr.	0·2 to 0·6 gm.
" Lactas . . .	15 to 60 gr.	1 to 4 gm.
" Phosphas . . .	10 to 30 gr.	0·6 to 2 gm.
Calomel . . .	1/2 to 3 gr.	0·08 to 0·2 gm.
Calx Sulphurata . . .	1/4 to 1 gr.	0·016 to 0·2 gm.
Camphora . . .	2 to 5 gr.	0·12 to 0·3 gm.
* " Monobromata . . .	2 to 8 gr.	0·12 to 0·5 gm.
*Cannabinæ Tannas . . .	4 to 8 gr.	0·25 to 0·5 gm.
*Capsicinum . . .	1/20 to 1/8 gr.	0·008 to 0·008 gm.
*Cerebrin . . .	5 to 20 gr.	0·8 to 1·2 gm.
*Cerii Oxalas . . .	2 to 10 gr.	0·12 to 0·6 gm.
*Chinosol . . .	1 to 5 gr.	0·06 to 0·3 gm.
Chlorbutol . . .	5 to 20 gr.	0·8 to 1·2 gm.
Cinchophenum . . .	5 to 15 gr.	0·8 to 1 gm.
Chloralis Hydras . . .	5 to 20 gr.	0·8 to 1·2 gm.
Chloroformum . . .	1 to 5 min.	0·06 to 0·3 c.cm.
Cocainæ Hydrochloridum . .	1/8 to 1/4 gr.	0·008 to 0·016 gm.
Codeina ; Codeinæ Phosphas	1/4 to 1 gr.	0·016 to 0·06 gm.
Copaiba . . .	10 to 30 min.	0·6 to 2 c.cm.
*Cotarninæ Hydrochloridum	1/8 to 1½ gr.	0·02 to 0·09 gm.
Creosotum . . .	2 to 10 min.	0·12 to 0·6 c.cm.
Creta . . .	15 to 60 gr.	1 to 4 gm.
Cupri Sulphas (emetic) . .	5 to 10 gr.	0·8 to 0·6 gm.
Diamorphinæ Hydrochlor . .	1/24 to 1/8 gr.	0·0025 to 0·008 gm.
*Didymin . . .	5 gr. and upwards	0·8 gm. and upwards
*Digituinum (Amorph.) . .	1/100 to 1/30 gr.	0·0006 to 0·002 gm.
* " (Cryst.) . . .	1/500 to 1/180 gr.	0·00018 to 0·0005 gm.
*Digoxin . . .	—	0·00025 to 0·0005 gm.
*Elaterinum . . .	1/40 to 1/10 gr.	0·0015 to 0·006 gm.
Elixir Cascariæ Sagradæ . .	30 to 60 min.	2 to 4 c.cm.
Emetinæ et Bismuthi Iodidum	1 to 3 gr.	0·06 to 0·2 gm.
* " Hydrobromidum . . .	1/6 to 1/2 gr.	0·01 to 0·08 gm.
" Hydro- (expect) . . .	1/100 to 1/30 gr.	0·0006 to 0·002 gm.
chloridum (emetic) . . .	1/12 to 1/6 gr.	0·005 to 0·01 gm.
*Ephedrina . . .	1/4 to 2 gr.	0·016 to 0·12 gm.

	IMPERIAL	METRIC
Ephedrinæ Hydrochloridum	1/4 to 1½ gr.	0'016 to 0'1 gm.
Ergota Præparata	5 to 15 gr.	0'3 to 1 gm.
*Ergotoxina	1/100 to 1/50 gr.	0'00065 to 0'0018 gm.
Ergotoxinæ Æthanosulphonas (subcutaneously or intramuscularly)	1/120 to 1/60 gr.	0'0005 to 0'001 gm.
*Erythrityl Tetranitras	1/4 to 1 gr.	0'015 to 0'06 gm.
Eucalyptol	1 to 8 min.	0'06 to 0'2 c.cm.
*Ext. Aloes	1 to 4 gr.	0'06 to 0'25 gm.
„ Belladonnæ Siccum	1/4 to 1 gr.	0'015 to 0'06 gm.
„ Cascaræ Sagradæ Liq.	1/2 to 1 dr.	2 to 4 c.cm.
„ „ „ Sicc.	2 to 8 gr.	0'12 to 0'5 gm.
„ Cinchonæ „	2 to 8 gr.	0'12 to 0'5 gm.
„ „ „ Liq.	5 to 15 min.	0'3 to 1 c.cm.
„ Colchici Sicc.	1/4 to 1 gr.	0'015 to 0'6 gm.
„ „ „ Liq.	2 to 5 min.	0'12 to 0'3 c.cm.
„ Colocynthis Comp.	2 to 8 gr.	0'12 to 0'5 gm.
* „ Ergotæ	2 to 8 gr.	0'12 to 0'5 gm.
„ „ „ Liq.	10 to 20 min.	0'6 to 1'2 c.cm.
* „ Euonymi	1 to 2 gr.	0'06 to 0'12 gm.
„ Fellis Bovini	5 to 15 gr.	0'3 to 1 gm.
„ Filicis	45 to 90 min.	3 to 6 c.cm.
„ Gentianæ	2 to 8 gr.	0'12 to 0'5 gm.
„ Hamamelidis Liq.	30 to 60 min.	2 to 4 c.cm.
„ Hepatis Liq.	1 fl. oz.	30 c.cm.
„ „ Siccum	quantity equivalent to ½ lb. or 225 gm. fresh liver	
* „ Hydrastis Liq.	5 to 15 min.	0'3 to 1 c.cm.
„ Hyoscyami Sicc.	1/4 to 1 gr.	0'016 to 0'06 gm.
„ „ „ Liq.	3 to 6 min.	0'2 to 0'4 c.cm.
„ Nucis Vomice Liq.	1 to 3 min.	0'06 to 0'2 c.cm.
„ „ „ Sicc.	1/4 to 1 gr.	0'015 to 0'06 gm.
„ Opii Siccum	1/4 to 1 gr.	0'015 to 0'06 gm.
„ Senegæ Liq.	5 to 15 min.	0'3 to 1 c.cm.
„ Sennæ Liq.	10 to 30 min.	0'6 to 2 c.cm.
*Fel Porcinum Purificatum	5 to 15 gr.	0'3 to 1 gm.
Ferri Carbonas Saccharatus	10 to 30 gr.	0'6 to 2 gm.
„ et Ammonii Citras	5 to 15 gr.	0'3 to 1 gm.
„ et Quinina Citras	5 to 15 gr.	0'3 to 1 gm.
* Glycerophosphas	1 to 5 gr.	0'06 to 0'3 gm.
* Hypophosphis	1 to 5 gr.	0'06 to 0'3 gm.
* „ Iodidum	1 to 5 gr.	0'06 to 0'3 gm.
„ „ Pyrophosphas	2 to 8 gr.	0'12 to 0'5 gm.
„ Sulphas	1 to 5 gr.	0'06 to 0'3 gm.
„ Sulphas Exsiccatus	1/2 to 3 gr.	0'03 to 0'2 gm.
* „ Valerianas	1 to 5 gr.	0'06 to 0'3 gm.
Ferrum Reductum	1 to 10 gr.	0'06 to 0'6 gm.
*Gelsemina Hydrochloridum	1/60 to 1/20 gr.	0'001 to 0'008 gm.
*Glycerinum Pepsini	1 to 2 dr.	4 to 8 c.cm.
Glyceryl Trinitras	1/130 gr. (approx.)	0'0005 gm.
*Guaiaci Resina	5 to 15 gr.	0'3 to 1 gm.
Guaiacol	5 to 10 min.	0'3 to 0'6 c.cm.
* „ Camphoras	5 to 10 gr.	0'3 to 0'6 gm.

	IMPERIAL.	METRIC
*Guaiacol Carbonas	5 to 15 gr.	0·3 to 1 gm.
*Hæmoglobin	5 to 30 gr.	0·3 to 2 gm.
*Heroin Hydrochloridum (see Diamorphine)		
Hexamina	10 to 30 gr.	0·6 to 2 gm.
Homatropinæ Hydro-		
bromidum	1/64 to 1/32 gr.	0·001 to 0·002 gm.
*Hydrargyri Iodidum Flavum	1/8 to 1/2 gr.	0·008 to 0·08 gm.
Iodidum Rubrum	1/32 to 1/16 gr.	0·002 to 0·004 gm.
* Iodidum Viride	1/6 to 1 gr.	0·01 to 0·06 gm.
Perchloridum	1/32 to 1/16 gr.	0·002 to 0·004 gm.
Subchloridum	1/2 to 3 gr.	0·08 to 0·2 gm.
Hydrargyrum c̄ Creta	1 to 5 gr.	0·06 to 0·3 gm.
*Hydrastinæ Hydrochloridum	1/4 to 1 gr.	0·016 to 0·06 gm.
*Hydrastinæ Hydro-		
chloridum	1/4 to 1/2 gr.	0·016 to 0·08 gm.
Hyoscinæ Hydrobromidum	1/200 to 1/100 gr.	0·0008 to 0·0006 gm.
*Hyoscyaminæ Sulphas	1/200 to 1/100 gr.	0·0008 to 0·0006 gm.
Ichthyol (Ichthammol)	5 to 10 gr.	0·3 to 0·6 gm.
Insulin	5 to 100 units	—
Iodoformum	1/2 to 3 gr.	0·03 to 0·2 gm.
Ipecacuanha { (expect.)	1/2 to 2 gr.	0·03 to 0·12 gm.
Pulverata { (emetic)	15 to 30 gr.	1 to 2 gm.
Jalapa Pulverata	5 to 20 gr.	0·3 to 1·2 gm.
*Jalapæ Resina	2 to 5 gr.	0·12 to 0·8 gm.
*Kurchi Bark	15 gr. gradually increased to 60 gr. daily	1 gm. gradually increased to 4 gm. daily
*Leptandrinum	2 to 5 gr.	0·12 to 0·8 gm.
Liquor Adrenalinæ Hydroch.	2 to 8 min.	0·12 to 0·5 c.cm.
Ammonii Acet. Dil.	2 to 8 dr.	5 to 30 c.cm.
Arsenicalis (Fowler)	2 to 8 min.	0·12 to 0·5 c.cm.
* Arsenici Hydrochlor.	2 to 8 min.	0·12 to 0·5 c.cm.
Arseni et Hydrarg. {		
Iodidi (Donovan) }	5 to 15 min.	0·3 to 1 c.cm.
* Bism. et Ammon. Cit	1/2 to 1 dr.	2 to 4 c.cm.
Ergosterolis Irradiati		
prophylactic	5 to 15 min.	0·3 to 1 c.cm.
curative	25 to 50 min.	1·5 to 3 c.cm.
* Ferri Dialysatus	10 to 30 min.	0·6 to 1·8 c.cm.
Perchloridi	5 to 15 min.	0·3 to 1 c.cm.
Glycerilis Trinitratis	1/2 to 2 min.	0·08 to 0·12 c.cm.
Hydrarg. Perchlor	1/2 to 1 dr.	2 to 4 c.cm.
Iodi Mitis	5 to 30 min.	0·3 to 2 c.cm.
Simplex	8 to 15 min.	0·2 to 1 c.cm.
Morphinæ Acetatis ...	10 to 60 min.	0·6 to 3·6 c.cm.
Hydrochlor.	5 to 30 min.	0·3 to 2 c.cm.
* Tartratis	10 to 60 min.	0·6 to 3·6 c.cm.
Potassii Hydroxidi	10 to 30 min.	0·6 to 1·8 c.cm.
Quinina Ammoniatas	1/2 to 1 dr.	2 to 4 c.cm.
Strychninæ Hydrochl.	5 to 12 min.	0·2 to 0·8 c.cm.
*Lithii Benzoas ; Lithii Citras	5 to 10 gr.	0·3 to 0·6 gm.
* Carbonas	2 to 5 gr.	0·12 to 0·3 gm.
* Salicylas	10 to 30 gr.	0·6 to 2 gm.

	IMPERIAL	METRIC
Magnesi Carbonas, <i>Levis vel</i> Pond.	10 to 60 gr.	0·6 to 4 gm.
Magnesi Oxidum Leve	{ 10 to 60 gr.	0·6 to 4 gm.
" Oxidum Pond.		
" Sulphas	80 to 240 gr.	2 to 16 gm.
*Manganesii et Ferri Citras	8 to 10 gr.	0·2 to 0·6 gm.
* " Peroxidum	... 2 to 10 gr.	0·13 to 0·6 gm.
*Medulla Ossis	... 5 to 80 gr.	0·3 to 2 gm.
Menthol	1/2 to 2 gr.	0·08 to 0·12 gm.
Methyl Salicylas	... 5 to 15 min.	0·3 to 1 c.cm.
Methylsulphonal	... 5 to 20 gr.	0·8 to 1·2 gm.
Methylthioninæ Chloridum	1 to 5 gr.	0·06 to 0·8 gm.
*Morphinæ Acetas, *Hypo- phosphis, *Sulphas	{ 1/8 to 1/2 gr.	0·008 to 0·08 gm.
Morphinæ Hydrochlorid.	1/8 to 1/8 gr.	0·008 to 0·02 gm.
" Tartras	1/8 to 1/8 gr.	0·008 to 0·02 gm.
Nux Vomica Pulverata	1 to 4 gr.	0·06 to 0·25 gm.
*Oleum Crotonis	1/2 to 1 min.	0·08 to 0·06 c.cm.
" Eucalypti	1 to 8 min.	0·06 to 0·2 c.cm.
* " Gaultheriæ	5 to 15 min.	0·3 to 1 c.cm.
* " Juniperi	1/2 to 3 min.	0·08 to 0·2 c.cm.
" Menthæ Pip.	1 to 3 min.	0·06 to 0·2 c.cm.
" Ricini	1 to 4 dr.	4 to 16 c.cm.
" Santali	{ ...	0·3 to 1 c.cm.
" " <i>Australiensis</i>		
" " <i>Terebinthinæ</i>	8 to 10 min.	0·2 to 0·6 c.cm.
" " <i>(Anthelmintic)</i>	120 to 240 min.	8 to 16 c.cm.
Opium Pulveratum	1/2 to 8 gr.	0·08 to 0·2 gm.
*Ovarian Substance	... 5 to 10 gr.	0·3 to 0·6 gm.
Orthocaina	1½ to 8 gr.	0·1 to 0·2 gm.
Pancreatinum	8 to 10 gr.	0·2 to 0·6 gm.
*Papainum	2 to 10 gr.	0·12 to 0·6 gm.
Paraffinum Liquidum	2 to 8 dr.	7·5 to 30 c.cm.
Paraldehydum	1/2 to 2 dr.	2 to 8 c.cm.
Pelletierinæ Tannas	2 to 8 gr.	0·12 to 0·5 gm.
Pepsinum	5 to 10 gr.	0·3 to 0·6 gm.
Phenacetinum	5 to 10 gr.	0·3 to 0·6 gm.
Phenazonum	... 5 to 10 gr.	0·3 to 0·6 gm.
Phenobarbitone	1/2 to 2 gr.	0·08 to 0·12 gm.
Phenol	... 1 to 8 gr.	0·06 to 0·2 gm.
Phenolphthaleinum	1 to 5 gr.	0·06 to 0·3 gm.
*Phosphorus	... 1/100 to 1/25 gr.	0·0006 to 0·0025 gm.
Physostigminæ Salicylas	1/100 to 1/50 gr.	0·0006 to 0·0012 gm.
* " Sulphas	1/64 to 1/82 gr.	0·001 to 0·002 gm.
*Picrotoxinum	... 1/100 to 1/25 gr.	0·0006 to 0·0025 gm.
*Pilocarpinæ Hydrochloridum	1/20 to 1/5 gr.	0·008 to 0·012 gm.
" Nitras	... 1/20 to 1/5 gr.	0·008 to 0·012 gm.
Pil. Aloes	... 4 to 8 gr.	0·25 to 0·5 gm.
" " et Asafetidæ	... 4 to 8 gr.	0·25 to 0·5 gm.
" " et Ferri	... 4 to 8 gr.	0·25 to 0·5 gm.
* " Colocynthis Comp.	... 4 to 8 gr.	0·25 to 0·5 gm.
" " et Hyoscyami	4 to 8 gr.	0·25 to 0·5 gm.
" Ferri Carbonatis	... 5 to 80 gr.	0·3 to 2 gm.

	IMPERIAL	METRIC
*Pil. Galbani Comp.	4 to 8 gr.	0'25 to 0'5 gm.
„ Hydrargyri	4 to 8 gr.	0'25 to 0'5 gm.
„ Rhei Comp.	4 to 8 gr.	0'25 to 0'5 gm.
* „ Saponis Comp.	2 to 4 gr.	0'12 to 0'25 gm.
*Piperazine	5 to 15 gr.	0'3 to 1 gm.
*Piperinum	2 to 8'gr.	0'12 to 0'5 gm.
*Pituitary Gland Substance	2 to 6 gr.	0'18 to 0'4 gm.
* „ (Posterior Lobe) Extract	2 to 15 units	
Plumbi Acetas	1/2 to 2 gr.	0'08 to 0'12 gm.
Podophylli Resina	1/4 to 1 gr.	0'015 to 0'06 gm.
Potassii Acetas	15 to 60 gr.	1 to 4 gm.
„ Bicarbonas	15 to 60 gr.	1 to 4 gm.
* „ Bichromas	1/10 to 1/5 gr.	0'006 to 0'012 gm.
„ Bromidum	5 to 30 gr.	0'3 to 2 gm.
„ Carbonas	2 to 5 gr.	0'12 to 0'3 gm.
„ Chloras	5 to 10 gr.	0'3 to 0'6 gm.
„ Citras	15 to 60 gr.	1 to 4 gm.
* „ Hypophosphis	1 to 5 gr.	0'06 to 0'3 gm.
„ Iodidum	5 to 30 gr.	0'3 to 2 gm.
„ Permanganas	1 to 3 gr.	0'06 to 0'2 gm.
* „ Tartras	30 to 240 gr.	2 to 16 gm.
„ Tartras Acidus	15 to 60 gr.	1 to 4 gm.
Procainæ Hydrochloridum	1/2 to 2 gr.	0'08 to 0'12 gm.
*Prostate Gland Substance	2 to 5 gr.	0'13 to 0'3 gm.
*Pulvis Antimonialis	8 to 6 gr.	0'2 to 0'4 gm.
* „ Catechu Comp.	10 to 60 gr.	0'6 to 4 gm.
* „ Cinnamomi Comp.	10 to 60 gr.	0'6 to 4 gm.
„ Cretæ Aromaticus	10 to 60 gr.	0'6 to 4 gm.
„ „ Aromaticus & Opio	10 to 60 gr.	0'6 to 4 gm.
„ Glycyrrh Comp.	60 to 120 gr.	4 to 8 gm.
„ Ipecacuanhæ et Opia	5 to 10 gr.	0'3 to 0'6 gm.
„ Jalapæ Comp.	10 to 60 gr.	0'6 to 4 gm.
„ Rhei Comp.	10 to 60 gr.	0'6 to 4 gm.
Quinidinæ Sulphas	3 to 10 gr.	0'2 to 0'6 gm.
*Quininæ Acetylsalicylas	1 to 5 gr.	0'06 to 0'3 gm.
„ Bisulphas	1 to 10 gr.	0'06 to 0'6 gm.
„ Dihydrochloridum	1 to 10 gr.	0'06 to 0'6 gm.
* „ et Æthylis Carbonas	1 1/2 to 15 gr.	0'1 to 1 gm.
* „ Hydrobromidum	1 to 10 gr.	0'06 to 0'6 gm.
„ Hydrochlor., vel Sulph.	1 to 10 gr.	0'06 to 0'6 gm.
* „ Hypophosphis	1 to 5 gr.	0'06 to 0'3 gm.
* „ Lactas	1 to 5 gr.	0'06 to 0'3 gm.
* „ Salicylas	1 to 5 gr.	0'06 to 0'3 gm.
* „ Valerianas	1 to 3 gr.	0'06 to 0'2 gm.
*Residuum Rubrum	5 gr. and upwards	0'3 gm. and upwards
Resorcinol	1 to 5 gr.	0'06 to 0'3 gm.
Salicinum	5 to 15 gr.	0'3 to 1 gm.
*Salol	5 to 20 gr.	0'3 to 1'2 gm.
Santoninum	1 to 3 gr.	0'06 to 0'2 gm.
Scopolamina (see) Hyoscina		
*Sodii Arsenas Anhydrosus	1/40 to 1/10 gr.	0'0015 to 0'006 gm.
„ Benzoes	5 to 30 gr.	0'3 to 2 gm.

	IMPERIAL	METRIC
Sodii Bicarbonas ...	15 to 60 gr.	1 to 4 gm.
„ Bromidum ..	5 to 80 gr.	0·8 to 2 gm.
* „ Cacodylas ...	1/4 to 1 gr.	0·016 to 0·06 gm.
„ Citras ...	15 to 60 gr.	1 to 4 gm.
* „ Glycerophosphas ...	5 to 10 gr.	0·8 to 0·6 gm.
* „ Hypophosphis ...	8 to 10 gr.	0·2 to 0·6 gm.
„ Iodidum • ...	5 to 80 gr.	0·8 to 2 gm.
„ Nitris ...	1/2 to 2 gr.	0·08 to 0·12 gm.
„ Phosphas ..	80 to 240 gr.	2 to 16 gm.
„ „ Acidus ..	80 to 60 gr.	2 to 4 gm.
„ „ Effervescens ...	60 to 240 gr.	4 to 16 gm.
„ Salicylas ...	10 to 80 gr.	0·6 to 2 gm.
„ Sulphas ...	80 to 240 gr.	2 to 16 gm.
„ „ Effervescens ..	60 to 240 gr.	4 to 16 gm.
* „ Sulphis ...	5 to 20 gr.	0·8 to 1·2 gm.
* „ Sulphocarbolas ...	5 to 15 gr.	0·8 to 1 gm.
*Sparteine Sulphas (orally) ..	1 to 2 gr.	0·06 to 0·18 gm.
Spiritus Ætheris ...	15 to 60 min.	1 to 4 c.cm.
„ Ætheris Nitrosi ...	15 to 60 min.	1 to 4 c.cm.
„ Ammon. Arom. ...	15 to 60 min.	1 to 4 c.cm.
„ Camphoræ ...	5 to 80 min.	0·8 to 2 c.cm.
„ Chloroformi ...	5 to 80 min.	0·8 to 2 c.cm.
*Spleen Substance ...	5 to 15 gr.	8/8 to 1 gm.
*Strychnina ...	1/64 to 1/16 gr.	0·001 to 0·004 gm.
Strychninæ Hydrochlor. ...	1/82 to 1/8 gr.	0·002 to 0·008 gm.
* „ Nitras vel Sulphas ...	1/64 to 1/16 gr.	0·001 to 0·004 gm.
Sulpharsphenamina ...	1½ to 10 gr.	0·1 to 0·6 gm.
Sulphonal ...	5 to 20 gr.	0·8 to 1·2 gm.
Sulphur Præcip. vel Sublim. ...	15 to 16 gr.	1 to 4 gm.
*Suprarenal Gland ...	5 gr. and upwards	0·8 gm. and upwards
*Syrupus Codeinæ Phosphatis ...	1/2 to 2 dr.	2 to 8 c.cm.
Syrupus Ferri Iodidi ...	1/2 to 2 dr.	2 to 8 c.cm.
„ „ Phosphatis Co. ...	1/2 to 2 dr.	2 to 8 c.cm.
„ „ Phosph. c. ...	1/2 to 1 dr.	2 to 4 c.cm.
Quin. et Strych. (Easton) }		
Terebenum ...	5 to 15 min.	0·8 to 1 c.cm.
Thymol ...	1/2 to 2 gr.	0·08 to 0·12 gm.
„ (anthelmintic) ...	15 to 80 gr.	2 to 2 gm.
*Thymus Gland ..	5 to 25 gr.	0·8 to 1·5 gm.
Thyroideum ...	1/2 to 5 gr.	0·08 to 0·8 gm.
Thyroxine-sodium ...	1/640 to 1/64 gr.	0·0001 to 0·001 gm.
Tinctura Belladonnæ ...	5 to 80 min.	0·8 to 2 c.cm.
„ Capsici ...	5 to 15 min.	0·8 to 1 c.cm.
„ Cinchonæ ...	1/2 to 1 dr.	2 to 4 c.cm.
„ Cinchonæ Comp. ...	1/2 to 1 dr.	2 to 4 c.cm.
„ Digitalis ...	5 to 15 min.	0·8 to 1 c.cm.
„ „ (single) ...	80 to 90 min.	2 to 6 c.cm.
* „ Gelsemii ...	5 to 15 min.	0·8 to 1 c.cm.
* „ Guaiaci Ammon. ...	1/2 to 1 dr.	2 to 4 c.cm.
* „ Hamamelidis ...	1/2 to 1 dr.	2 to 4 c.cm.
* „ Hydrastis ...	1/2 to 1 dr.	2 to 4 c.cm.
* „ Hyoscyami ...	1/2 to 1 dr.	2 to 4 c.cm.
„ Ipecacuanhæ ...	10 to 80 min.	0·6 to 2 c.cm.

	IMPERIAL.	METRIC
Tinctura Ipecacuanhæ (emetic)	1/2 to 1 oz.	15 to 30 c.cm.
„ Krameriæ	30 to 60 min.	2 to 4 c.cm.
„ Lobelia Ætheriæ	5 to 15 min.	0·8 to 1 c.cm.
„ Nucis Vomiciæ	10 to 30 min.	0·6 to 2 c.cm.
„ Opii	5 to 30 min.	0·3 to 2 c.cm.
„ „ Camphorata	1/2 to 1 dr.	2 to 4 c.cm.
„ Quassiæ	30 to 60 min.	2 to 4 c.cm.
* „ Quinini	1/2 to 1 dr.	2 to 4 c.cm.
„ Rhei. Comp.	1/2 to 1 dr.	2 to 4 c.cm.
„ Scillæ	5 to 30 min.	0·3 to 2 c.cm.
„ Stramonii	5 to 30 min.	0·3 to 2 c.cm.
„ Strophanthi	2 to 5 min.	0·12 to 0·3 c.cm.
„ Tolutana	1/2 to 1 dr.	2 to 4 c.cm.
„ Valerianæ Ammon.	1/2 to 1 dr.	2 to 4 c.cm.
* „ Warburgi	1 to 4 dr.	4 to 15 c.cm.
„ Zingiberis Mitis	1/2 to 1 dr.	2 to 4 c.cm.
„ „ Foetidis	5 to 10 min.	0·3 to 0·6 c.cm.
Totaquina	1 to 10 gr.	0·06 to 0·6 gm
Trinitrophenol (Picric acid)	1 to 5 gr.	0·06 to 0·3 gm
*Trional (Methylsulphonal)	5 to 20 gr.	0·3 to 1·2 gm.
*Urotropine	5 to 15 gr.	0·3 to 1 gm.
*Veronal (Barbitone)	5 to 16 gr.	0·3 to 0·6 gm.
*Vinum Carnis et Ferri	1 to 4 dr.	3·5 to 16 c.cm
* „ Ipecac. { (expectorant)	10 to 30 min.	0·6 to 1·3 c.cm.
„ „ { (emetic)	1 to 6 dr.	16 to 24 c.cm.
*Zinci Acetas	1 to 2 gr.	0·06 to 0·12 gm.
„ Sulphas (emetic)	10 to 30 gr.	0·6 to 2 gm.
* „ Valerianas	1 to 8 gr.	0·06 to 0·2 gm.

Hypodermic Posological Table

	IMPERIAL	METRIC
*Aconitinæ Nitræs	1/640 gr.	0'0001 gm.
Adrenalina	1/600 to 1/120 gr.	0'0001 to 0'0005 gm.
Apomorphinæ Hydrochlor.	1/32 to 1/8 gr.	0'002 to 0'0028 gm.
Atropinæ Sulphas	1/200 to 1/100 gr.	0'0003 to 0'0006 gm
*β-Eucainæ Hydrochlor., <i>vel Lactas</i> }	1/8 to 1/2 gr.	0'008 to 0'03 gm
*Bulbocapninæ Phosphas	1½ gr.	0'1 gm.
Caffeina et Sodii-benzoas	2 to 5 gr.	0'12 to 0'8 gm.
*Caffeinæ Sodio-salicylas	1 to 5 gr.	0'06 to 0'8 gm.
Cocainæ Hydrochloridum	1/8 to 1/4 gr.	0'008 to 0'016 gm.
Codeinæ Phosphas	1/4 to 1 gr.	0'016 to 0.06 gm.
*Cotarninæ Hydrochloridum.	1/4 to 1/2 gr	0'016 to 0'08 gm.
*Curara	1/12 to 1/2 gr.	0'005 to 0'08 gm.
Diamorphinæ Hydrochlor.	1/24 to 1/8 gr.	0'0025 to 0'0008 gm.
*Digitalinum (Amorph.)	1/100 to 1/80 gr.	0'0006 to 0'002 gm.
" (Cryst.)	1/500 to 1/180 gr.	0'00018 to 0'0005 gm.
*Digoxin	—	0.5 mgm. in 1 c.cm. to 1 mgm. in 2 c.cm.

	IMPERIAL	METRIC
Emetinæ Hydrochloridum	$\frac{1}{2}$ to 1 gr.	0'08 to 0'06 gm.
*Ephedrina	$\frac{1}{2}$ to 2 gr.	0'032 to 0'012 gm.
Ephedrinæ Hydrochloridum	$\frac{1}{4}$ to 1 gr.	0'016 to 0'1 gm.
Ergotoxinæ Æthanosulphonas	$\frac{1}{120}$ to $\frac{1}{60}$ gr.	0'0005 to 0'001 gm.
*Glycerilis Trinitras	$\frac{1}{250}$ to $\frac{1}{50}$ gr.	0'00025 to 0'0018 gm.
*Heroin Hydrochloridum (<i>see</i> Diamorphine, above)		
Hamatropinæ	$\frac{1}{64}$ to $\frac{1}{32}$ gr.	0'001 to 0'002 gm.
Hydrobromidum {		
" Hydrochlor.	$\frac{1}{64}$ to $\frac{1}{32}$ gr.	0'001 to 0'002 gm.
* Hydrarg. Perchloridum	$\frac{1}{160}$ to $\frac{1}{80}$ gr.	0'001 to 0'002 gm.
* " Succinimidum	$\frac{1}{6}$ to $\frac{1}{4}$ gr.	0'01 to 0'015 gm.
Hyoscine Hydrobromidum	$\frac{1}{200}$ to $\frac{1}{100}$ gr.	0'0008 to 0'0006 gm.
*Hyoscyaminæ Sulphas	$\frac{1}{200}$ to $\frac{1}{100}$ gr.	0'0003 to 0'0006 gm.
Injections, P.B.—		
Bismuthi	8 to 15 min.	0'5 to 1 c.cm.
" Salicyl.	10 to 20 min.	0'6 to 1'2 c.cm.
Ferri	15 to 30 min.	1 to 2 c.cm.
Hydrargyri	5 to 10 min.	0'3 to 0'6 c.cm.
" Subchloridi	10 to 20 min.	0'6 to 1'2 c.cm.
Morphinæ Hydrochloridum	$\frac{1}{8}$ to $\frac{1}{3}$ gr.	0'008 to 0'02 gm.
* " Hypophosp., Meconas	$\frac{1}{8}$ to $\frac{1}{2}$ gr.	0'008 to 0'03 gm.
* " Phosphas vel Sulphas	$\frac{1}{8}$ to $\frac{1}{2}$ gr.	0'008 to 0'03 gm.
" Tartras	$\frac{1}{8}$ to $\frac{1}{3}$ gr.	0'008 to 0'02 gm.
*Ouabain	$\frac{1}{1000}$ to $\frac{1}{250}$ gr.	0'00006 to 0'00025 gm.
Physostigminæ Salicylas	$\frac{1}{100}$ to $\frac{1}{50}$ gr.	0'0006 to 0'0012 gm.
*Picrotoxinum	$\frac{1}{100}$ to $\frac{1}{25}$ gr.	0'0006 to 0'0025 gm.
Pilocarpinæ Nitras	$\frac{1}{20}$ to $\frac{1}{5}$ gr.	0'003 to 0'012 gm.
Procainæ Hydrochloridum		
<i>Subcutaneously</i>	up to 15 gr.	up to 1 gm.
<i>Intrathecally</i>	up to 2½ gr.	up to 0'15 gm.
Quininæ Bisulphas	1 to 10 gr.	0'06 to 0'6 gm.
" Dihydrochloridum	5 to 10 gr.	0'3 to 0'6 gm.
* " Hydrobromidum	$\frac{1}{2}$ to 2 gr.	0'03 to 0'18 gm.
* " Lactas	1 to 5 gr.	0'06 to 0'3 gm.
*Sparteine Sulphas	$\frac{1}{6}$ to 1 gr.	0'01 to 0'06 gm.
Strophanthinum	$\frac{1}{240}$ to $\frac{1}{60}$ gr.	0'00025 to 0'001 gm.
Strychninæ Hydrochloridum	$\frac{1}{200}$ to $\frac{1}{16}$ gr.	0'0003 to 0'004 gm.
* " Nitras vel Sulphas	$\frac{1}{200}$ to $\frac{1}{16}$ gr.	0'0003 to 0'004 gm.

PRESCRIPTIONS

(The following prescriptions are mainly based on the Pharmacopœa of the School of Tropical Medicine, Calcutta)

BATHS (Balnæ)

Alkaline bath (Balneum alkalinum). Sodium bicarbonate 1 oz., water (warm) 6 gal.

Bran bath (Balneum furfuris). Wheaten bran 2 oz., water (100° F.) 1 gal. Bran is tied in a muslin bag which is put into the bath.

Sulphur bath (Balneum sulphuris). Precipitated sulphur 2 oz., sodium thiosulphate 1 oz., dilute sulphuric acid $\frac{1}{2}$ oz., water up to 1 pint. Each pint to be added to a bath containing 30 gal. of water at 90° to 100° F.

CAPSULES (Capsulæ)

Chenopodium capsule (Capsulæ chenopodii). Oil of chenopodium 10 min. in each. Dose—3 capsules (one every hour).

Creosote capsule (Capsulæ creosoti). Creosote 1 to 5 min. in each.

Gentian violet capsule (Capsulæ methylrosanilini). Gentian violet 1 gr. in each.

Hexylresorcinol capsule (Capsulæ hexylresorcinolis). Hexylresorcinol 15 gr. in hard gelatin capsules (to be freshly filled up).

CAUSTICS (Caustica)

Silver nitrate caustic (Causticum argenti nitras). Silver nitrate 1 in 10 solution. Sticks may also be used

Trichloroacetic acid caustic (Causticum trichloroaceticum). Trichloroacetic acid 1 in 3 solution. It is applied lightly with a brush till the part painted appears to be uniformly whitish.

COLLODION (Collodium)

Collodion of chrysarobin (Collodium chrysarobinum). Chrysarobin $\frac{1}{2}$ dr., salicylic acid 20 gr., collodion 1 oz

CONFECTIONS (Confectionis)

Confection of senna (Confectio sennæ). Powdered senna 90 gr., jalap 30 gr., ginger 10 gr., coriander oil $\frac{1}{2}$ min., treacle (by weight) up to 1 oz. Dose—1 to 2 dr.

Confection of sulphur (Confectio sulphuris). Sublimed sulphur $\frac{1}{2}$ oz., potassium acid tartrate 1 dr., treacle (by weight) 1 oz. Dose—1 to 2 dr

The strengths of the solutions used in these prescriptions correspond to those in B. P. 1932.

CREAMS (Cremoris)

Calamine cream (Cremor calaminæ). Zinc oxide $\frac{1}{2}$ dr., prepared calamine $\frac{1}{2}$ dr., lime water 4 dr., almond oil up to 1 oz.

Magnesium sulphate cream (Cremor magnesiæ sulphatæ.) Magnesium sulphate 24 oz., phenol 1 dr., glycerine 12 oz. Heat Mag. Sulph. to 100°C., powder while hot. Add glycerine and phenol gradually.

DRAUGHTS AND MIXTURES**DRAUGHTS (Haustus)**

Anthelmintic draught (Haustus anthelminticus). Chenopodium oil 16 min., tetrachlorethylene 48 min., magnesium sulphate draught 2 oz. Mix and shake vigorously immediately before use.

Aperient draught * (Haustus sennæ compositus). Magnesium sulphate $2\frac{1}{2}$ dr., spirit of chloroform 10 min., infusion of senna up to 1 oz.

Bromide draught (Haustus bromidi). Potassium bromide 10 gr., sodium bromide 10 gr., compound tincture of cardamom $\frac{1}{2}$ dr., peppermint water up to 1 oz.

Carbon tetrachloride draught (Haustus carboni tetrachloridi). Carbon tetrachloride 48 min., magnesium sulphate draught 2 oz. Mix and shake vigorously immediately before use.

Chloral and bromide draught (Haustus chloral et bromidi). Chloral hydrate 15 gr., potassium bromide 15 gr., liquid extract of liquorice 2 min., chloroform water up to 1 oz.

Lupulus and bromide draught (Haustus lupulus et bromidi). Tincture of lupulus 1 dr., potassium bromide 10 gr., spirit of chloroform 10 min., water up to 1 oz.

Magnesium sulphate draught (Haustus magnesiæ sulphatis). Magnesium sulphate 4 dr., citric acid 5 gr., peppermint water up to 2 oz.

Morphine draught (Haustus morphinæ). Solution of morphine hydrochloride 1 dr., water up to 1 oz.

Paraldehyde draught (Haustus paraldehydum). Paraldehyde 2 dr., syrup of orange 1 dr., chloroform water up to 1 oz.

Sodium sulphate draught (Haustus sodii sulphatis). Sodium sulphate 4 dr., peppermint water 1 oz.

Stimulant draught (Haustus stimulans). Spirit of ether 20 min., aromatic spirit of ammonia 1 dr., compound tincture of cardamom 1 dr., spirit of chloroform 10 min., water up to 1 oz.

MIXTURES (Misturæ)

Alkaline mixture (Mistura alkalina). Sodium bicarbonate 15 gr., sodium citrate $\frac{1}{2}$ dr., chloroform water up to 1 oz.

Ammonium chloride mixture (acid) (Mistura ammonii chloridi acidæ). Ammonium chloride 10 gr., dilute hydrochloric acid 10 min.,

magnesium sulphate 30 gr., liquid extract of liquorice 30 min., chloroform water up to 1 oz.

Ammonium chloride mixture (alkaline) (*Mistura ammonii chloridi alkalina*). Ammonium chloride 10 gr., sodium citrate 20 gr., liquid extract of liquorice 30 min., chloroform water up to 1 oz.

Asthma mixture (*Mistura asthmatica*). Potassium iodide 3 gr., potassium bicarbonate 5 gr., tincture of belladonna 5 min., ethereal tincture of lobelia 10 min., chloroform water up to 1 oz.

Asthma mixture with ephedra (*Mistura asthmatica cum ephedrina*). Tincture of ephedra 20 min., asthma mixture up to 1 oz.

Asthma mixture with kuth (*Mistura asthmatica cum kuth*). Liquid extract of kuth $\frac{1}{2}$ dr., asthma mixture up to 1 oz.

Basham's mixture (*Mistura ferri perchloridi composita*). Solution of perchloride of iron 15 min., dilute acetic acid 20 min., solution of ammonium acetate 2 dr., glycerine $\frac{1}{2}$ dr., water up to 1 oz.

Bismuth mixture (*Mistura bismuthi*). Bismuth oxy-carbonate 15 gr., sodium bicarbonate 15 gr., compound tragacanth powder 10 gr., chloroform water 1 oz.

Calcium lactate mixture (*Mistura calcii lactatis*). Calcium lactate 10 gr., chloroform water up to 1 oz.

Carminative mixture (*Mistura carminativa*). Magnesium carbonate (heavy) 10 gr., aromatic spirit of ammonia 30 min., spirit of chloroform 20 min., compound tincture of cardamom 25 min., cinnamon water up to 1 oz.

Carminative mixture with rhubarb (*Mistura carminativa cum rheo*). Tincture of rhubarb 10 min., sodium bicarbonate 10 gr., peppermint oil $\frac{1}{2}$ min., spirit of ether 10 min., aromatic spirit of ammonia 15 min., chloroform water up to 1 oz.

Chalk mixture (*Mistura cretæ co.*). Aromatic powder of chalk 20 gr., tincture of catechu 30 min., syrup of ginger 30 min., peppermint water up to 1 oz.

Charcoal mixture (*Mistura carbonis ligni*). Charcoal 1 dr., liquified phenol 2 min., chloroform water 1 oz.

Cholagogue mixture (*Mistura sodii sulphatis co.*). Sodium sulphate 30 gr., sodium phosphate 20 gr., sodium salicylate 10 gr., sodium bicarbonate 20 gr., sodium benzoate 10 gr., spirit of chloroform 10 min., distilled peppermint water up to 1 oz.

Cinchona febrifuge mixture (*Mistura cinchoninæ*). Cinchona febrifuge 10 gr., citric acid 20 gr., magnesium sulphate 1 dr., water 1 oz.

Cinnamon mixture (*Mistura cinnamomi*). Cinnamon oil 30 min., acacia gum 2 gr., syrup of tolu 30 min., water up to 1 oz.

Codeine mixture (*Mistura codeinæ*). Codeine phosphate $\frac{1}{2}$ gr., sodium sulphate 1 dr., liquid extract of jambul 1 dr., tincture of nuxvomica 5 min., glycerine of glycerophosphate, 1 dr., compound infusion of gentian up to 1 oz.

Creosote mixture (*Mistura creosote*). Creosote 2 min., acacia 1 gr., lemon oil $\frac{1}{2}$ min., gluside $\frac{1}{2}$ gr., water up to 1 oz.

Diaphoretic mixture (*Mistura diaphoretica*). Potassium acetate 20 gr., potassium citrate $\frac{1}{2}$ dr., solution of ammonium acetate 2 dr., spirit of nitrous ether 10 min., chloroform water up to 1 oz.

Diuretic mixture (*Mistura diuretica*). Potassium acetate 10 gr., potassium citrate 30 gr., liquid extract of punarnava 1 dr., infusion of buchu up to 1 oz.

Dysentery mixture (*Mistura dysenterica*). Magnesium sulphate $\frac{1}{2}$ dr., sodium sulphate $\frac{1}{2}$ dr., spirit of chloroform 5 min., cinnamon water up to 1 oz.

Expectorant mixture (sedative) (*Mistura expectorans sedativa*). Sodium bicarbonate 10 gr., compound tincture of camphor $\frac{1}{2}$ dr., tincture of ipecacuanha 10 min., syrup of tolu $\frac{1}{2}$ dr., chloroform water up to 1 oz.

Expectorant mixture (stimulant) (*Mistura expectorans stimulans*). Sodium bicarbonate 10 gr., ammonium carbonate 5 gr., tincture of squill 10 min., infusion of senega up to 1 oz.

Flatulence mixture. Menthol 4 gr., aromatic spirit of ammonia 1 oz., spirit of chloroform 1 oz. Dose—1 teaspoonful with water.

Gentian mixture (acid) (*Mistura gentianæ acida*). Dilute hydrochloric acid 15 min., tincture of nux vomica 5 min., compound infusion of gentian up to 1 oz.

Gentian mixture (alkaline) (*Mistura gentianæ alkalina*). Sodium bicarbonate 15 gr., tincture of nux vomica 5 min., infusion of rhubarb 4 dr., tincture of ginger 10 min., spirit of chloroform 10 min., compound infusion of gentian up to 1 oz.

Gentian and rhubarb mixture (*Mistura gentianæ cum rhei*). Peppermint oil 1 min., bicarbonate of soda 10 gr., tincture of nux vomica 5 min., spirit of chloroform 10 min., rhubarb infusion 4 dr., compound infusion of gentian up to 1 oz.

Hexamine mixture. No. I. Hexamine 1 gr., Orange Syrup $\frac{1}{2}$ dr., water up to 1 oz. No. II. acid sodium phosphate 20 gr., water up to 1 oz.

Hypophosphite mixture (*Mistura hypophosphite*). Calcium hypophosphite $7\frac{1}{2}$ gr., sodium hypophosphite $7\frac{1}{2}$ gr., glycerine 20 min., infusion of quasia up to 1 oz.

Iodide mixture (*Mistura potassii iodidi*). Potassium iodide 10 gr., potassium bicarbonate 10 gr., chloroform water up to 1 oz.

Iodide and salicylate mixture (*Mistura potassii iodidi et sodii salicylici*). Potassium iodide 5 gr., sodium salicylate 10 gr., sodium bicarbonate 10 gr., potassium bromide 5 gr., compound infusion of gentian up to 1 oz.

Iron mixture (*Mistura ferri*). Iron and ammonium citrate 30 gr., glycerine 20 min., water up to 1 oz.

Iron and arsenic mixture (*Mistura ferri arseni*). Iron and ammonium citrate 5 gr., arsenical solution 4 min., tincture of nux vomica 5 min., glycerine 10 min., water up to 1 oz.

Iron and digitalis mixture. Iron perchloride lotion 10 min., tincture of digitalis 10 min., dilute phosphoric acid 10 min., glycerine 10 min., distilled cinnamon water up to 1 oz.

Iron and strychnine mixture (*Mistura ferri et strychninæ*). Solution of ferric chloride 10 min., sodium sulphate 20 gr., strychnine hydrochloride solution 3 min., glycerine 15 min., water up to 1 oz.

Kaolin mixture (*Mistura kaolini*). Kaolin 2 to 4 dr., cinnamon water 1 oz. or more.

Mercuric biniodide mixture (*Mistura hydrargyri biniodidi*). Solution of mercuric chloride $\frac{1}{2}$ dr., potassium iodide 10 gr., compound tincture of cardamom 20 min., water up to 1 oz.

Mercuric chloride mixture (*Mistura hydrargyri perchloridi*). Solution of mercuric chloride $\frac{1}{2}$ dr., compound tincture of cardamom 20 min., water up to 1 oz.

Quinine mixture (*Mistura quininæ*). Quinine sulphate 10 gr., citric acid 15 gr., spirit of chloroform 10 min., water up to 1 oz.

Sodium salicylate mixture (*Mistura sodii salicylas*). Sodium salicylate 10 gr., sodium bicarbonate 20 gr., water up to 1 oz.

Tonic mixture (bitter) (*Mistura amara*). Dilute phosphoric acid 15 min., tincture of nux vomica 5 min., spirit of chloroform 10 min., compound infusion of gentian up to 1 oz.

Triple carbonate mixture (*Mistura Tricarbonatum*). Sodium bicarbonate 10 gr., bismuth oxy carbonate 10 gr., magnesium carbonate (heavy) 10 gr., peppermint water 1 oz.

Triple sulphate mixture (*Mistura ferri aperiens*). Ferrous sulphate 2 gr., quinine sulphate 3 gr., magnesium sulphate 1 dr., arsenical solution 2 min., dilute sulphuric acid 5 min., peppermint water up to 1 oz.

Valerian mixture (*Mistura valerianæ*). Tincture of ammoniated valerian $\frac{1}{2}$ dr., potassium bromide 10 gr., spirit of cajuput 5 min., chloroform water up to 1 oz.

White mixture (*Mistura alba*). Magnesium sulphate 1 dr., magnesium carbonate (heavy) 10 gr., peppermint water up to 1 oz.

Yellow mixture (*Mistura flava*). Sodium bicarbonate 10 gr., infusion of gentian 1 oz.

DRINKS (*Potus*)

Imperial drink (*Potus imperialis*). Acid potassium tartrate 60 gr., juice of half a fresh lemon, sufficient sugar, boiling water 1 pint. Infuse, stirring occasionally till cold, then strain.

Ispaghula drink (*Potus ispaghulae*). Ispaghula $\frac{1}{2}$ to 1 oz., cold water 1 pint. Soak for 2 hours.

DROPS (*Guttæ*)

Alkaline drop (*ear*) (*Guttæ alkalinae*). Sodium bicarbonate 20 gr., borax 20 gr., glycerine 2 dr., water up to 1 oz.

Carbolic drop (*ear*) (*Guttæ phenolis*). Liquified phenol 5 min., rectified spirit $\frac{1}{2}$ oz., water $\frac{1}{2}$ oz.

Cocaine and carbolic acid drop (*ear*) (*Guttæ cocainæ et phenolis*). Liquified phenol 5 min., cocaine hydrochloride 5 gr., menthol 5 gr., glycerine 1 oz.

Homatropine drop (*eye*) (*Guttæ homatropinae*). Homatropine hydrobromide 4 gr., distilled water 1 oz.

Spirit drop (*ear*) (*Guttæ spiritus*). Glycerine of boric acid and rectified spirit in equal parts.

Zinc sulphate drops (*eye*) (*Guttæ zinci sulphatis*). Zinc sulphate 2 dr., boric acid 4 gr., distilled water 1 oz.

EMULSIONS (*Emulsiones*)

Castor oil emulsion (*Emulsio oleum ricini*). Castor oil 1 dr., mucilage of acacia 1 dr., compound tincture of cardamom 20 min., peppermint water up to 1 oz.

Cod liver oil emulsion (*Emulsio olei morrhuae*). Cod liver oil 2 dr., mucilage of acacia 1 dr., glycerine 10 min., water up to 1 oz.

ENEMAS (*Enemata*)

Alkaline enema (*Enema alkalinum*). Sodium bicarbonate 1 dr., normal saline 1 pint.

Compound enema (*Enema compositum*). Tincture of asafoetida 30 min., castor oil $\frac{1}{2}$ to 1 oz., turpentine oil 1 to 2 dr., olive oil 4 dr., soap enema 2 pints.

Glucose enema (*Enema glucosæ*). Glucose 1 oz., sodium bicarbonate 1 dr., normal saline up to 1 pint. Dose—4 to 6 oz. (To be retained).

Glycerine enema (*Enema glycerinum*). Glycerine and warm water in equal parts. Glycerine 2 dr. to 1 oz. according to age.

Saline enema (*Enema saline*). Sodium chloride $1\frac{1}{2}$ dr., water 1 pint.

Soap enema (*Enema saponis*). Soft soap 1 oz., water 2 pints.

Starch and opium enema (*Enema amyli cum opio*). Tincture of opium 30 min., mucilage of starch 2 pints. (To be retained).

FOMENTATION (*Fotus*)

Boric acid fomentation (*Fotus acidi borici*). Boric acid 6 dr., water (boiling) 1 pint.

GARGLES (Gargarismata)

Alum gargle (*Gargarisma aluminis*). Alum 10 gr., tincture of myrrh 5 min., water up to 1 oz.

Carbolic acid gargle (*Gargarisma phenolis*). Glycerine of carbolic acid 15 min., water up to 1 oz.

Chinosol gargle (*Gargarisma chinosolis*). Chinosol 2 gr., water 10 oz.

Potassium chlorate gargle (*Gargarisma potassii chloratis*). Potassium chlorate 10 gr., tincture of myrrh 5 min., water up to 1 oz.

Potassium permanganate gargle (*Gargarisma potassu permanganatis*). Potassium permanganate 1 dr., dilute sulphuric acid 15 min., water 8 oz.

INHALATIONS (Inhalationes)

Benzoin inhalation (*Inhalatio benzoini*). Compound tincture of benzoin 1 dr., water at 150°F. 1 pint. To be used in Nelson's inhaler.

Creosote inhalation (*Inhalatio creosoti*). Creosote 4 dr., chloroform 4 dr., menthol 10 gr., 10 drops in an inhaler every 2 hours.

Menthol and turpentine inhalation (*Inhalatio mentholis et terebinthinæ*). Menthol 1 dr., oil of turpentine 1 dr., chloroform 1 dr., rectified spirit 2 dr.

Pine oil inhalation (*Inhalatio pini*). Pine oil 5 min., magnesium carbonate (light) diffused in 1 dr. of water 4 gr., water at 150°F.

INJECTIONS (Injectiones)

Avenyl injection (*Injectio avenyl*). Avenyl 0.25 per cent. in oil hydnocarpus; 0.5 per cent. in ester.

Berberine injection (*Injectio berberis*). Berberine (acid) sulphate 2 per cent. solution in water. To be given subcutaneously around the ulcers.

Pituitrin and adrenalin injection (*Injectio pituitrinum et adrenalium*). Pituitrin 0.3 c.cm., adrenalin 0.2 c.cm. To be given intramuscularly.

Quinine injection (*intravenous*) *Injectio quinina*. Quinine bihydrobromide 7½ gr., sterile normal saline 20 c.cm. To be given very slowly.

INSUFFLATION (Insufflatio)

Ephedrine insufflation (*Insufflatio ephedrinæ*). Ephedrine alkaloid 5 gr., menthol 5 gr., camphor 5 gr., liquid paraffin up to 1 oz. Each constituent to be dissolved separately in a portion of liquid paraffin with gentle heat and mixed together.

LINCTUS (Linctus)

Diamorphine linctus (*Linctus diamorphinæ*). Diamorphine hydrochloride 1 gr., syrup of tolu 4 dr., syrup of virginian prune 4 dr., glycerine 3½ dr. Dose—¼ to 1 dr.

Paregoric linctus (*Linctus paregoricum*). Compound tincture of camphor, oxymel of squill, and syrup of tolu, in equal parts. Dose—1 teaspoonful.

Terpheroin linctus (*Linctus terpheroini*). Terpene hydrate 1 gr., acetomorphine hydrochloride 1/20 gr., menthol 1/20 gr., alcohol 10 min., glycerine 1 dr.

• **LINIMENTS (Linimenta)**

A. B. C. liniment (*Linimentum A. B. C.*). Liniment aconite, liniment belladonna and liniment chloroform, in equal parts.

Anodyne liniment (*Linimentum camphoræ et opii*). Camphor 10 gr., liniment of opium 2 dr., olive oil 1 oz.

Calamine liniment (compound) (*Linimentum calaminæ compositum*). Prepared calamine ½ dr., zinc oxide ½ dr., liquefied phenol 3 min., almond oil ½ oz., lime water up to 1 oz.

Calamine liniment (simple) (*Linimentum calaminæ simplex*). Olive oil 2 dr., calamine lotion up to 1 oz.

White liniment (*Linimentum album*). Olive oil 1 oz., solution of ammonia 1 oz., turpentine oil 1 oz.

Wintergreen liniment (*Linimentum gaultheriæ*). Oil of wintergreen 4 dr., menthol 2 dr., soft paraffin ½ oz., olive oil 1 oz.

LOTIONS (Lotiones)

Acridlavine lotion (*Lotio acridlavina*). Acridlavine 5 gr., water 1 pint.

Aluminium lotion (*Lotio aluminis*). Solution of aluminium acetate 1 dr., water 7 dr. It should be applied on plain gauze or muslin piece.

Bismuth and mercury lotion (*Lotio bismuthi et hydrargyri*). Bismuth oxynitrate 10 gr., mercuric chloride 1 gr., compound tragacanth powder 10 gr., water up to 1 oz.

Boric acid lotion (*Lotio acidi borici*). Boric acid 20 gr., water 1 oz.

Calamine lotion (*Lotio calaminæ*). Prepared calamine 2 dr., zinc oxide 1 dr., glycerine 20 min., lime water 1 oz.

Calamine lotion (compound) (*Lotio calaminæ composita*). Prepared calamine 1 dr., zinc oxide 1 dr., glycerine 1 dr., lead subacetate lotion (strong) 20 min., coal-tar solution 10 min., lime water up to 1 oz.

Eusol lotion (*Lotio eusol*). Eupad 4 dr. (consisting of equal parts of boric acid and bleaching powder), water 1 pint. To stand for 24 hours with frequent shaking and strain through muslin.

Gentian violet lotion (*Lotio methylrosanilini*). Gentian violet 20 gr., absolute alcohol 1 dr., water up to 1 oz.

Ichthyol lotion (*Lotio ichthyol*). Ichthyol 10 to 20 per cent. solution in water.

Lead lotion (*Lotio plumbi*). Lead subacetate lotion (strong) 10 min., glycerine 1 dr., water up to 1 oz.

Optochin lotion (*Lotio optochinum*). Ethyl hydrocupreine hydrochloride (optochin) 10 gr., water 1 pint.

Picric acid lotion (*Lotio acidi picrici*). Picric acid 25 gr., water 10 oz.

Red lotion (*Lotio rubra*). Zinc sulphate 2 gr., tincture of lavender 5 min., water up to 1 oz.

* **Resorcin lotion** (*Lotio resorcinolis*). Resorcin or euresol $\frac{1}{2}$ dr., spirit of ether $\frac{1}{2}$ dr., castor oil 10 min., rectified spirit $1\frac{1}{2}$ dr., water up to 1 oz.

* **Resorcin and mercury lotion** (*Lotio resorcinolis et hydrargyri*). Resorcin $\frac{1}{2}$ dr., sandal wood oil 5 min., mercuric chlorides $\frac{1}{2}$ gr. glycerine $\frac{1}{2}$ dr., rectified spirit 2 dr., water up to 1 oz.

Silver nitrate lotion (*Lotio argenti nitratis*). Silver nitrate 5 to 15 gr., spirit of ether 1 dr., distilled water 1 oz.

Sulphur lotion (compound) (*Lotio sulphuris composita*). Precipitated sulphur 1 dr., salicylic acid 10 gr., compound tragacanth powder .10 gr., water 1 oz.

Sulphur lotion (white) (*Lotio sulphuris alba*). Sulphuretted potassium 15 gr., zinc sulphate 15 gr., water up to 1 oz.

Sulphur lotion (yellow) (*Lotio sulphuris flava*). Precipitated sulphur 20 gr., absolute alcohol 2 dr., glycerine 10 min., lime water 2 dr., water up to 1 oz.

Tannic acid lotion (*Lotio acidi tannici*). Tannic acid 12 gr., water up to 1 oz.

Zinc and copper sulphate lotion (*Lotio zinci et cupri*). Zinc sulphate 6 gr., copper sulphate 6 gr., water 1 oz.

Zinc sulphate lotion (*Lotio zinci sulphatis*). Zinc sulphate 10 gr., water 1 oz.

NOSE WASH (*Collunarium*)

Alkaline nose wash (*Collunarium alkalinum*). Sodium bicarbonate 15 gr., sodium chloride 15 gr., borax 15 gr., sugar 30 gr., water 1 oz. Mix two tablespoonfuls with double the quantity of tepid water and sniff.

OIL (*Oleum*)

Catheter oil (*Oleum lubricans*). Phenol 1 dr., castor oil 4 dr., almond oil $2\frac{1}{2}$ oz.

*For gray or light-haired person use euresol instead of resorcin.

OINTMENTS (Unguenta)

Acridiflavine ointment (1 in 1,000) (Unguentum acridiflavini). Acridiflavine $\frac{1}{2}$ gr., vaseline 1 oz.

Beta-naphthol ointment (Unguentum beta-naphtholis). Beta-naphthol 30 gr., vaseline 1 oz.

Bismuth ointment (Unguentum bismuthi). Bismuth oxychloride 15 gr., olive oil 2 dr., liquefied phenol 10 min., soft paraffin up to 1 oz.

Boric acid ointment (Unguentum acidi boric). Boric acid 1 dr., vaseline 1 oz.

Brilliant green ointment. Brilliant green 10 gr., rectified spirit 1 dr., soft paraffin 1 oz.

Compound chrysarobin ointment (Unguentum chrysarobin co.). Chrysarobin 40 gr., ichthylol 30 gr., salicylic acid 30 gr., vaseline up to 1 oz.

Dilute ammoniated mercury ointment (Unguentum hydrargyri ammoniati dilutum). Ammoniated mercury 5 to 10 gr., soft paraffin 1 oz.

Ichthylol ointment (Unguentum ichthyolis). Ichthylol 1 part, paraffin ointment 9 parts.

Mercuric nitrate ointment (Unguentum hydrargyri nitratis) Mercuric nitrate 40 gr., olive oil 4 dr., liquid paraffin 4 dr.

Resorcin ointment (Unguentum resorcinolis). Resorcin $\frac{1}{2}$ dr., vaseline 1 oz.

Resorcin and mercury ointment (Unguentum resorcinolis et hydrargyri). Resorcin $\frac{1}{2}$ dr., mercuric chloride 2 gr., zinc oxide ointment 1 oz.

Rose ointment (Unguentum rosæ). Lanolin 1 part, white wax 1 part, almond oil 2 parts, rose water 2 parts.

Salicylic acid ointment (Unguentum acidi salicylici). Salicylic acid 30 gr., vaseline 1 oz.

Sulphur ointment (Unguentum sulphuris). Sublimed sulphur 1 dr., vaseline 1 oz.

Tar and salicylic ointment (Unguentum picis cum acido salicylico). Solution of coal tar $\frac{1}{2}$ to 1 dr., salicylic acid 30 gr., zinc oxide 15 gr., vaseline 1 oz.

Whitfield ointment (Unguentum acidi salicylici et benzoici). Salicylic acid 15 gr., benzoic acid 15 gr., cocoanut oil 4 dr., lanolin 4 dr.

Wintergreen ointment (Unguentum gaultheriæ). Oil of wintergreen 2 dr., menthol 1 dr., vaseline up to 1 oz.

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PAINTS (Pigmenta)

Aconite paint (Pigmentum aconiti). Tincture of aconite 2 dr., tincture of myrrh 2 dr., tincture of iodine 2 dr.

Alum Paint (Pigmentum aluminis). Alum 10 gr., dilute sulphuric acid 1 oz.

Belladonna paint (Pigmentum belladonnæ). Green extract of belladonna 4 dr., glycerine 4 dr.

Chrysarobin paint (Pigmentum chrysarobini). Chrysarobin 40 gr., gutta percha 1 dr., chloroform 1 oz.

Creosote and salicylic acid paint (Pigmentum creosotæ cum acido-salicylico). Salicylic acid 2 dr., creosote 2 dr., glycerine up to 1 oz.

Formalin paint (Pigmentum formaldehydi). Formalin $\frac{1}{2}$ dr., glycerine 1 oz.

Ichthyol and belladonna paint (Pigmentum ichthyolis et belladonnæ). Ichthyol 2 dr., green extract of belladonna 2 dr., glycerine up to 1 oz.

Iron paint (Pigmentum ferri perchloridi). Solution of perchloride of iron 4 dr., glycerine 4 dr.

Lichen paint. Resorcin $1\frac{1}{2}$ dr., salicylic acid 1 dr., phenol 1 dr., mercuric chloride 5 gr., glycerine 1 dr., rectified spirit 5 dr., water 5 dr.

Mandl's paint (Pigmentum Mandl). Iodine 6 gr., potassium iodide 20 gr., peppermint oil 5 min., glycerine 1 oz.

Menthol paint (Pigmentum mentholis). Menthol 2 dr., camphor 2 dr., chloral hydrate 2 dr.

Resorcin and benzoin paint (Pigmentum resorcinolis et benzoini). Resorcin $\frac{1}{2}$ dr., compound tincture of benzoin 1 oz.

Resorcin and carbolic paint (Pigmentum resorcinolis et phenolis). Resorcin $\frac{1}{2}$ dr., spirit of peppermint 20 min., liquefied phenol 3 min., glycerine up to 1 oz.

Resorcin and iron paint (Pigmentum resorcini et ferri). Resorcin 15 gr., menthol 4 gr., glycerine of perchloride of iron 1 oz.

Ringworm paint (Pigmentum tineæ). Resorcin 1 dr., salicylic acid 1 dr., liquefied phenol $\frac{1}{2}$ dr., glacial acetic acid 1 dr., glycerine 2 dr., compound tincture of benzoin 6 dr.

Salicylic acid paint (Pigmentum acidi salicylici). Salicylic acid 1 dr., extract of cannabis indica 10 gr., collodion flexile 1 oz.

PASTE (Pasta)

B. I. P. P. (Pasta bismuth et iodoformi). Bismuth subnitrate 1 dr., iodoform 2 dr., vaseline 5 dr.

Lassar's paste (Pasta lassari). Zinc oxide 2 dr., salicylic acid 10 gr., starch 2 dr., soft paraffin 4 dr. (Modified—zinc oxide 24 gr., starch 24 gr., lanolin $\frac{1}{2}$ oz., liquid paraffin $\frac{1}{2}$ oz.)

PILLS (Pillule)

Belladonna pill (compound) (Pillula belladonnæ composita). Extract of belladonna $\frac{1}{2}$ gr., menthol $\frac{1}{2}$ gr., extract of valerian 2 gr.

Codeine and cascara pill (Pillula codeinæ et cascariæ sagradæ). Codeine phosphate $\frac{1}{2}$ gr., aloin $\frac{1}{2}$ gr., extract of hyocyanus $\frac{1}{2}$ gr.,

extract of nux vomica $\frac{1}{2}$ gr., extract of euonymin 1 gr., extract of cascara sagrada 2 gr., glycerine with tragacanth—sufficient quantity.

Colocynth and mercury pill (compound) (*Pilula colocynthidis et hydrargyri composita*). Compound colocynth pill 3 gr., blue pill $\frac{1}{2}$ gr., extract of hyoscyamus 1 gr.

Iron arsenate pill (*Pilula ferri et arsenatis*). Iron arsenate $\frac{1}{10}$ gr., extract of nux vomica $\frac{1}{6}$ gr., quinine sulphate 2 gr., extract of gentian—sufficient quantity.

Quarter grain pill (*Pilula aloinæ composita*). Aloin $\frac{1}{2}$ gr., podophyllin $\frac{1}{2}$ gr., extract of nux vomica $\frac{1}{2}$ gr., iridin $\frac{1}{2}$ gr., extract of gentian—sufficient quantity.

POULTICES (Cataplasmata)

Kaolin poultice (antiphlogistine) (*Cataplasma kaolini*). Kaolin $\frac{1}{2}$ oz., boric acid 20 gr., thymol 1 gr., wintergreen oil 1 min., peppermint oil 1 min., glycerine 1 oz. Heat kaolin on water bath for 1 hour and then add the rest.

Linseed poultice (*Cataplasma lini*). Crushed linseed 4 oz., water (boiling) 10 oz. Add slowly crushed linseed to the boiling water constantly stirring and spread $\frac{1}{2}$ inch thick layer on lint or calico.

Starch poultice (*Cataplasma amvli*). Starch 1 oz., boiling water 10 oz. Make a paste with a little cold water and then add boiling water.

POWDERS (Pulveres)

A. P. C. powder (*Pulvis A. P. C.*). Aspirin 5 gr., phenacetin 2 gr., caffeine citrate 3 gr.

Bismuth and ipecacuanha powder (*Pulvis bismuthi et ipecacuanhæ*). Bismuth salicylate 10 gr., compound ipecacuanha powder 5 gr.

Calamine powder (*Pulvis calaminæ*). Prepared calamine 2 dr., camphor 1 dr., starch 1 oz.

Calomel powder (*Pulvis calomel*). Calomel $\frac{1}{2}$ gr., Sodium bicarbonate 5 gr. Dose—one powder every half hour till three or four such to be followed by a saline purgative.

Carbonate powder (double) (*Pulvis carbonatum duplicatum*). Bismuth oxycarbonate 1 oz., sodium bicarbonate $\frac{1}{2}$ oz. Dose—one teaspoonful.

Carbonate powder (triple) (*Pulvis carbonatum triplicatum*). Bismuth oxycarbonate 1 oz., magnesium carbonate (heavy) 1 oz., sodium bicarbonate $\frac{1}{2}$ oz. Dose—one teaspoonful. Maclean's powder contains calcium carbonate as well.

Rhubarb powder (*Pulvis rhei*). Powdered rhubarb root 10 gr., sodium bicarbonate 2 gr., powdered ginger 2 gr.

Santonin powder (compound) (*Pulvis santoninum compositum*). Santonin 3 gr., calomel 2 gr., sodium bicarbonate 5 gr.

Sulphur and camphor powder (*Pulvis sulphuris et camphoræ*). Camphor 1 oz., precipitated sulphur 1 oz., zinc oxide 1 oz., boric acid 1 oz., starch 4 oz., kaolin 2 oz.

Zinc and boric powder (*Pulvis zinci et acidi borici*). Boric acid, zinc oxide and starch in equal parts.

SPIRITS (*Spiritus*)

Mercury spirit (*Spiritus hydrargyri perchloridi*). Mercuric chloride 2 gr., alcohol 70 per cent. 1 oz.

Soap spirit (*Spiritus saponis*). Soft soap 1 oz., rectified spirit 2 oz. To be used as a shampoo.

SPRAY (*Nebula*)

Alkaline spray (*Nebula alkalina*). Sodium bicarbonate, sodium chloride and borax, each 15 gr., phenol 5 gr., spirit of peppermint 15 min., glycerine 1 dr., water up to 1 oz.

Compound eucalypti spray (*Nebula eucalypti composita*). Oil of eucalyptus 3 min., oil of cinnamon 3 min., thymol 3 gr., chloretone 6 gr., menthol 3 gr., camphor 4 gr., liquid paraffin 1 oz.

NEW AND NON-OFFICIAL REMEDIES

Acetylcholine bromide. The drug is used in counteracting paralysis of the intestine after laparotomy and intestinal operations. It is useful in post-operative gas distension and pain and to a certain extent to relieve acute constipation. It is also of value in certain types of vascular disturbances associated with arteriolar spasm. It is usually administered by intramuscular injection in doses of 0.1 gm. in 1 c.cm. of a solvent.

Albargin (*Silver gelatose*). This is a yellowish white powder containing gelatose (10 gm.). It is soluble in water and alcohol and contains 15 per cent. of silver. It is used in gonorrhœa in 0.2 per cent. solution (1 in 500) and is considered to be superior to protargol. It is efficacious when used as an instillation as 0.5 to 3 per cent. solution in ophthalmia neonatorum and phlyctenular conjunctivitis. In chronic bacillary dysentery encouraging results have been obtained by rectal injections of 30 gr. of the drug dissolved in 30 oz. of water. It is frequently used as a colonic lavage in ulcerative colitis with good results.

Alepoi. This is a selected fraction of the sodium salts of hydno-carpus acids. The powder is soluble in water and the solution is used for intramuscular and intravenous injections in leprosy. The usual dose for intramuscular and subcutaneous injections is 1 c.cm. of a 3 per cent. solution and for intravenous injections 1 c.cm. of a 1 per cent. solution increased by 1 c.cm. up to 5 or 10 c.cm. The injections are given twice a week.

Aptile-benzoic acid. It is a local analgesia, solution containing benzocaine (B.P.) 3 per cent., benzyl alcohol 5 per cent. and ether 10 per cent. in sterilised olive oil. The drug is injected in 2 c.cm. doses

round the vulvar region in pruritus vulvæ. Total injections number from 8 to 30, repeated at weekly intervals.

Aolan. See page 1418.

Argyrol (Vitellin). It is silver in combination with a wheat proteid and contains 30 per cent of silver. It forms a black solution in water. A 5 per cent. solution has proved valuable in gonorrhœa, but the drug is chiefly used in ophthalmic practice, instillations of 25 per cent. being painless and most reliable in gonorrhœal ophthalmia and ophthalmia neonatorum and acute conjunctivitis. It is used also as a 2 per cent. ointment with paraffin basis in eczematous conjunctivitis and keratitis and has been successfully injected in 1 per cent. solution in ulcerative colitis and dysentery.

Atebrin. See page 602.

Atebrin-musonat. This form of atebrin has come into prominence through trials made during the recent epidemic in Ceylon. It is simply an improved form of a soluble atebrin salt suitable for injection, the word 'musonat' being merely a fancy name coined for facility of laboratory reference. Trials of this form of atebrin have been made in Ceylon by Blaze (General Hospital, Colombo) and Simeons of Heidelberg who went to Ceylon for the purpose. Discussing the parenteral administration of atebrin, these workers refer to the findings of Hecht, who has shown that when atebrin is taken by the mouth much of it is retained in the upper intestine, liver, and bile, and that it circulates in these organs before reaching the peripheral blood. After continued administration a point is reached when the liver becomes saturated and the atebrin overflows into the peripheral circulation. It is known that atebrin when given orally has no effect on the clinical picture for some days. It has also been suggested that toxic symptoms, when they appear, are caused by an exceptionally high concentration of atebrin in the liver and upper intestine. If these conjectures are correct, parenteral administration of atebrin should have an immediate effect, and this intramuscular injection caused no toxic or unpleasant symptoms. A single injection of 0.375 gm. had a remarkable effect on the clinical picture, but recrudescence usually occurred in a few days. Two similar injections on successive days, however, proved sufficient to control the temperature within forty-eight hours, and in four days all forms of benign tertian parasites, and the ring forms of malignant tertian, were destroyed. Crescents are not affected and must be destroyed by plasmoquine. The intravenous route is harmless, but is not satisfactory for routine treatment. The relapse rate after atebrin-musonat has yet to be studied.

Atophan (Phenyl quinoline-carboxylic acid). It increases uric acid output and hence is used in gouty arthritis. *Dose.*—7½ gr., two or three times a day. An alkaline mixture is given along with this drug. See also novatophan.

Avenyl. It is a compound of mercury for the treatment of leprosy complicated with syphilis. It is given in the form of a 0.25 per cent. solution in hydnocarpus oil or a 0.5 per cent. solution in moogrol, of which 1 c.cm. increased to 4 c.cm. or more, is injected subcutaneously.

Avertin or tribromethyl alcohol. It has recently come into use as a basal anæsthetic for rectal administration. It is a white crystalline substance requiring protection from light and air to avoid decomposition. Avertin is rapidly absorbed by the rectal mucous membrane, is non-irritant and induces a smooth anæsthesia free from excitement and lasting for about two hours. About $1\frac{1}{2}$ to 3 gr. for each $2\frac{1}{5}$ lb. body weight are required and injected as a 3 per cent. solution in distilled water or physiological saline. The full degree of anæsthesia is attained in about half an hour, and if not deep enough may be supplemented by gas and oxygen or ether. This is required in about two thirds of patients when less than 2 gr. per $2\frac{1}{5}$ lb. body-weight are given. It is wise to avoid its use where hepatic disease is present, though the evidence that avertin itself affects hepatic function is yet uncertain. It has been used in eclampsia with success. Rectal diseases, peritonitis and cachectic conditions are also contra-indications to its use.

Bayer 205. See page 466.

Bee venom. It is a preparation containing the venom of bee stings for the treatment of rheumatism. The major part of the protein is fixed and discarded during the process of manufacture and the venom is suspended in normal saline containing 0.5 per cent. of phenol. Bee venom is supplied as a course of 12 ampoules containing progressively stronger doses. The first ampoule contains the equivalent of half a normal bee sting, this dose being known as 5 units. The injection should be given well under the skin to avoid local reaction.

Benzyl benzoate or spasmodin. It is a liquid though the pure salt is a solid. A number of benzyl esters lowers the tonus of smooth muscles and are relatively non-toxic. All these substances have been used in a variety of conditions in which the spasm of smooth muscle is present such as colics, dysmenorrhœa, asthma, whooping cough, etc. Benzyl benzoate is given in emulsion containing 2 to 5 min. in each dose. Benzyl formate and succinate are given in doses up to 20 gr.

Berberine sulphate. See page 451.

Bicreol. See page 727.

Bile salts. Taurocholate and glycocholate of sodium, from ox-bile, have been used as solvents for gall-stones and in chronic constipation and dyspepsia. Sodium taurocholate has been recommended for gouty obesity and dyspepsia in doses of 2 to 6 gr. in keratin coated pills. Sodium glycocholate appears to be a useful cholagogue for congestion of the liver, gall-stones, constipation and melancholia in doses of 2 to 6 gr. Infantile marasmus has been treated with bile salts, average dose is $\frac{1}{2}$ gr. of the mixed salts for infants of three months.

Bouchi oil (*Psorale corylifolia*). It is used externally for leucoderma.

Bromural or bromigene. It is a monobrom-iso-valerianyl urea, in white crystals. This substance possesses very marked hypnotic powers beyond the small amount of bromine (36 per cent.) contained in its full hypnotic dose of 10 gr., the sedative action being mainly due to its isopropyl constitution. It induces apparently natural sleep within about 20 minutes with safety, and without producing any untoward effects. It has been given in 2 gr. doses with benefit in whooping cough and various neurotic conditions, but it has no narcotic action. The drug is best given in tablets or dissolved in hot liquid when a speedy effect is

desired. It has proved valuable in epilepsy, neuroses occurring at the menopause and in sea-sickness.

Calcium gluconate. It contains (anhydrous) 9.3 per cent. of calcium. It is indicated in diseases requiring calcium therapy. Taken by mouth, it is well absorbed. Given intramuscularly it is painless and non-irritant. It is better tolerated than calcium chloride when given intravenously. It is said to be almost specific in hay fever and extensively used in many respiratory diseases, debility, malnutrition, neurasthenia and other affections. The oral dose is 1 to 2 dr. three times a day and for intramuscular or intravenous injections it is given in doses of 10 c.cm. of a 10 per cent. solution.

Campolon. It is an extract of the effective factor of liver tissue, which on clinical trial has proved highly efficacious in macrocytic anæmias and is free from all by-effects. It is prepared for administration by intramuscular injections; 2 c.cm. is equivalent to 500 gm. of fresh liver.

Cannabinon. It is a purified and very soft resin obtained from Indian hemp. It occasionally proves inert. It has been given with good results in the sleeplessness of mania in doses of $\frac{1}{2}$ to 1 gr. rubbed up with sugar of milk. *Haschischen* is the name given to a brownish powder prepared from the alcoholic extract, which is variable in its effects.

Carbarson. See page 411.

Carbo ligni. It is a powerful oxidising agent, owing to the amount of oxygen absorbed by it, and it is used as an antidote in poisoning by phosphorus and by alkaloids such as morphine, strychnine, etc., rendering them inert. Half ounce of it neutralises 1 gr. of the alkaloid but its administration should not interfere with the use of the stomach pump, emetics and purgatives, which should follow. Internally, wood charcoal is administered in flatulent conditions of the stomach and intestines as an absorbent and deodoriser.

Cardiazol. See page 249.

Casein. It is the albuminoid substance present in milk and constitutes the chief bulk of cheese. It is employed as the basis of many artificial foods as Plasmon, Virogen, Casumen, Nutrose, etc. The last mentioned substance consists of pure caseinate of sodium, 1 oz. of which dissolved in a pint of heated milk, may be used as a food in marasmus, diarrhoea and stomach diseases.

Catechu. It is a valuable local astringent and may be used as gargles or lozenges for spongy gums, mercurial and ulcerative stomatitis. The action of the drug is exactly like tannic acid and is a useful remedy for diarrhoea when combined with opium, kino and chalk. The usual dose is 5 to 15 gr.

Cerium oxalate. This and also the sulphocarbolate have been used in the vomiting of pregnancy, some forms of gastric irritation, in chronic diarrhoea, hysteria, epilepsy and migraine. They are white powders given in 3 gr. doses with an equal amount of powdered sugar.

Chaulmoogra oil and its derivatives. See page 923.

Chlorotone. It is a hypnotic, local anæsthetic and anti-emetic.
Dose.—5 to 20 gr.

Cignolin. It is dioxyanthranol, a non-staining preparation of chrysophanic acid. It forms an useful external application in psoriasis in strengths of $\frac{1}{2}$ to 1 per cent. solution in benzol or acetone.

Colchicine. It is the active principle of colchicum, suitable for hypodermic injection in $\frac{1}{32}$ gr. doses in painful joint affections, chronic rheumatism, and gouty troubles. Colchicine salicylate, which is now obtainable in capsules, containing $\frac{1}{250}$ gr. dissolved in methyl salicylate, is also known as Colchisal.

Coramine (Pyridine- β -carbonic acid diethylamide). It is a synthetic substance having a camphor-like action. It is used in shock, cardiac asthenia following infectious diseases, arteriosclerosis, renal affections, bronchial asthma, poisoning with narcotics and asphyxia of the new-born. The drug is held to be a substitute for camphor, strychnine and caffeine since in cases of collapse it has a stimulating action on the central nervous system and on the circulatory and respiratory apparatus. It is water soluble. *Dose.*—1 to 2 c.cm. of the liquid, with a little water orally; 1 to 2 ampoules (each 1.1 c.cm.) hypodermically, intramuscularly or intravenously.

Cryogenin (Meta-benzamine-semicarbazide). It is a crystalline, sparingly soluble coal-tar derivative, with antipyretic properties resembling those possessed by phenacetin. It has been given in 3 to 24 gr. doses. The drug is a useful antipyretic in fevers.

Cyclopropane. Lucas and Henderson (1929) first suggested the use of cyclopropane or trimethylene as an anæsthetic agent. It is a colourless gas possessing a sweetish odour and is inflammable. The gas is available compressed in steel bottles at a pressure of 75 lb. The gas is administered by the method of a closed circuit employing carbon dioxide absorption with an oxygen percentage greater than 20. The usual practice is to employ a cyclopropane-oxygen mixture. In the absence of high oxygen concentrations respiratory failure is apparently produced when the proportion of cyclopropane rises to 45 per cent. Anæsthesia produced by the drug is quiet with a good muscular relaxation. Premedication with morphine and hyoscine reduces the amount of cyclopropane necessary to secure full surgical anæsthesia. Recovery is rapid and excepting nausea and vomiting post-anæsthetic complications are rare. The anæsthetic is of particular value in thoracic surgery.

Damiana. This name is given to a drug (*Turnera diffusa*, var. *aphrodisiaca*) long used by the Mexicans as a stimulant to the reproductive centres. The leaves and flowers are the parts used in medicine as aphrodisiac. It has been tried with some success in melancholia. It is a mild laxative and bitter. Good results have been obtained from it in cases of sexual debility and hypochondriasis. *Dose.*—1 dr. of the fluid extract (1 in 1), or 2 to 8 gr. of the extract. The drug is also said to be tonic and diuretic.

Decholin. It consists of dihydrochloric acid, an oxidation product of cholic acid derived from natural bile acids. Both it and its sodium salt are used in functional insufficiency of the liver, to outline the bile ducts at operation, and in cholecystography to accelerate the appearance of the gall bladder shadow and to hasten the removal of the

residual 'opacol' from the biliary apparatus, in cardiac decompensation with hepatic congestions, cirrhosis of the liver and similar conditions associated with ascites. *Dose*.—4 to 8 gr., three times daily after meals for a period of 4 to 6 weeks.

Digifortis (in ampoules). Each ampoule contains 1 c.cm. of a solution that presents the whole of the active principles of digitalis without inert matter. Each ampoule contains the equivalent of one digifortis tablet *gr* 10 min. of the liquid digifortis for oral use. The activity of digifortis solution in each c.cm. ampoule is 0.8 international unit. By the mouth it is given in doses of 15 to 30 min.

Digoxin. It is a pure glucoside of digitalis prepared from the Austrian foxglove, *Digitalis lanata*. It is absorbed and eliminated more rapidly than digitalis. The drug is mainly indicated in cases of auricular fibrillation with a high ventricular rate with or without congestive failure sometimes attended with severe vomiting and where a rapid response to treatment is required. It can be administered both orally and intravenously. The initial dose, depending upon the body weight of the patient, is 1.00, 1.25 or 1.50 mgm. (4 to 6 tablets each containing 0.25 mgm.), followed six hours later by 0.25 mgm., and then the same dose every six hours until the ventricular rate falls to 60 to 70 per minute. The intravenous dose is 0.75 to 1.00 mgm., and this can be followed after an interval of 4 to 6 hours by digoxin given by mouth.

Divinyl ether. Divinyl oxide, divinyl ether, vinethene as it is called represents ethylene plus ether and is used as an anæsthetic. It is a colourless liquid more volatile than ether and possessing a sweetish ethereal odour. It is less irritating to the respiratory tract and can be administered either by the open drop method or by the closed method with or without carbon dioxide. The anæsthesia is characterised by rapid induction and quick recovery. The rate of administration during induction by the open method should be about one drop per second and the average amount necessary for the maintenance of anæsthesia is 2 c.cm per minute. Muscular relaxation is complete within a short time the anæsthetic is administered. Post anæsthetic complications are also never marked.

Emmenin complex. This is an orally active cestrogenic hormone derived from the placenta. It is regarded as a hydrolysable complex of trihydroxy-cestrin, the potency of which is increased in the presence of ovarian tissue. It supplements the cestrogenic activity of the hypo-functioning ovary and is indicated in the treatment of menopausal disturbances, menstrual headache, dysmenorrhœa and oligomenorrhœa. The usual dose is one teaspoonful daily in water.

Entero-vioform (Iodochlorhydroxy quinoline). The drug is a grayish yellow powder, almost insoluble in water and sparingly in alcohol; it contains 40 per cent. of iodine and is absorbed to some extent from the bowel as it is partly excreted in the urine. It is given orally in chronic amoebiasis and other parasitic intestinal diseases. The usual dose is 0.75 gm. daily in three capsules of 0.25 gm, each for ten days, the course being repeated after a week's rest to total 15 gm.

Glycine (Aminoacetic Acid). It is acetic acid with one of the hydrogen atoms replaced by the amino group. It is a white crystalline substance with a sweetish taste, readily soluble in water, non-toxic and

when administered orally acts as a diuretic like amino-acids in general. The drug has given encouraging result in the treatment of progressive muscular dystrophy, in myasthenia gravis and in similar conditions of deficient muscular tonus. The drug has been found to be more useful in myasthenia gravis when used in conjunction with ephedrine. *Dose*.—10 to 30 gr.

Ergosterol (irradiated). This is extensively used in diseases where vitamin D is indicated. Vitamin D is necessary to ensure calcium and phosphorus absorption for the treatment of rickets. The drug has also been suggested in the treatment of general spasmophilia, tetany, laryngismus stridulus, osteomalacia and certain idiopathic steatorrheas. *Dose*.—usually 2 to 5 mgm.

Eucortone and eschatin. These are two preparations of the active extract of suprarenal cortex used in the treatment of Addison's disease. It is now established that continued administration will restore and maintain good health in patients with Addison's disease. Patients in the stage of collapse should receive from 20 to 60 c.cm. daily, given in divided doses by intravenous injections.

Eukodal (Dihydroxy-codeinon hydrochloride). It has been introduced as a substitute for morphine. It is said to have a more rapid action, does not produce vomiting, and lead to tolerance upon repeated administrations. It is also less apt to produce constipation. *Dose*.—up to $\frac{1}{4}$ gr.

Euonymi cortex. The drug possesses tonic, hydragogue, cathartic, diuretic and antiperiodic properties. The drug has a cathartic effect resembling that of podophyllin but very much milder in action. *Dose*.—Euynmin—1 to 2 gr.; (chologogue) $\frac{1}{4}$ to 1 gr.; (cathartic) 1 to 4 gr.

Eupad (Pulvis calcis chlorinatæ et acidi boric). This name is given to equal amounts of dry chlorinated lime and boric acid, 25 parts of which are added to 1000 parts of water to form Rusol. Eupad was extensively used as a dry dressing to wounds during the war. It evolves hypochlorous acid rapidly in contact with water. It has been used intravenously in malignant endocarditis, puerperal septicæmia, pyæmia and other septic conditions.

Euphorbia pilulifera. Pill-bearing spurge, or Australian snake root, or cat's hair, is an asthma remedy. Good results are reported with it in dyspnoea of asthma, emphysema, bronchitis, and in dyspnoea of cardiac origin. It appears to act beneficially upon any kind of spasmodic dyspnoea, probably through its influence over the vagus, but its best effects are seen in ordinary spasmodic asthma, coryza and hay asthma. The gastric irritation arising from its administration can be avoided by giving the dose in a state of free dilution. One grain of the extract or 10 to 30 min. of the B. P. C. tincture (1 in 5 freely diluted) after meals, may be given 4 times a day.

Euphyllin. It is a combination of amphoteric theophylline with ethylenediamine, and is a crystalline yellowish white product containing about 80 per cent. of theophylline. It is distinguished from other purin bodies and particularly from theophylline and its salts by its ready solubility in water, its rapid absorption quality and its completely non-irritating powerful action. It is used as a diuretic, particularly in the

treatment of œdema of cardiac origin or when complicated with arterio sclerosis. Of particular significance is the fact that euphyllin surpasses all other purin bodies as a peripheral vasodilator. The remarkable vasodilatation of the coronary system accounts for the success obtained in the various manifestations of coronary sclerosis, angina pectoris, cardiac asthma, etc. It is administered orally, rectally, intravenously or intramuscularly and is supplied in the form of tablets containing 0.1 gm. ($\frac{1}{4}$ gr.) suppositories containing 0.36 gm. ($\frac{5}{8}$ gr.), or ampoules containing 0.48 gm. ($\frac{7}{8}$ gr.) in 2 c.cm. of distilled water.

Eusol (*Liquor acidi hypochlorosi compositus*). The solution contains approximately 0.27 per cent. hypochlorous acid with small amounts of calcium biborate and calcium chloride. The drug may be employed as a lotion or as a bath to wounds and has been extensively used during the war. The object is to secure the maximum effect with minimum irritation. Varicose ulcers, lacerated wounds, severe burns, cystitis (1 in 8 for irrigation), tuberculous sinuses and ulcers, hydatid cyst (douche with 2 pints half strength), septic cellulitis, tuberculous osteomyelitis, necrosis of the lower jaw, acute streptococcal infections, tuberculous empyema, gonorrhœal discharge (1 in 5), tonsillectomy (spray) were a few cases of the many cited by the medical research committee that were successfully treated with eusol and eupad.

Euquinine. See page 583.

Ferrox. It contains in each teaspoonful, ferrous iron 3 gr., (7 gr. of ferrous carbonate), yeast 30 gr., copper $\frac{1}{10}$ mgm., manganese $\frac{1}{10}$ mgm. and cobalt $\frac{1}{10}$ mgm. It is recommended for the treatment of microcytic anæmia and certain other forms of nutritional anæmias. It has been shown that small quantities of cobalt increase the size of the red blood cells, thus increasing the total volume of the blood. Manganese, it is claimed, reduces the toxic effect of the copper and cobalt and has a direct effect on the endocrine activity. The yeast is added to provide vitamin B. *Dose.*—1 to 2 teaspoonfuls twice or thrice daily before meals.

Ferratin. It is a reddish brown powder, consisting of iron (7 per cent.) in combination with albumin and is prepared from egg albumin and tartarated iron. It is claimed to be a food and the best form of substance for the administration of iron. *Dose.*—5 to 10 gr.

Fibrolysin. It is a double salt of thiosinamin and sodium salicylate and is a white crystalline powder, freely soluble in water. Thiosinamin itself is obtained from oil of mustard by the action of ammoniated alcohol, it is also known as Rhodallin, Allylsulpho-carbamide, and Allyl thio-urea. Fibrolysin is supplied in sterilised ampoules or glass capsules, containing about 40 min. of a 15 per cent. solution for one hypodermic dose corresponding to 3 gr. thiosinamin. Martindale's injection is composed of thiosinamin 20, antipyrine 33, eucaine lactate 0.65 and water to 100 parts and may be used in every case instead of fibrolysin in doses of 8 to 18 min. hypodermically. These injections were at one time considered to have great value in causing the absorption of pathological fibrous tissue.

Fermamint. It is the name given to tablets containing formaldehyde in combination with sugar of milk; they give off small quantities of formaldehyde in the mouth, and are employed in pharyngitis and

tonsillitis. Formolyptol is a composite mouth-wash containing various balsams combined with formaldehyde; its action resembles formosyl gargle, which contains essential oils with formaldehyde.

Fouadin. It is a complex trivalent antimony compound, stated to be sodium antimony pyrocatechin disulphonate of sodium. It is introduced for the treatment of bilharziasis and granuloma inguinale in place of antimony and potassium tartrate. Schistosomiasis is cured by intramuscular injections of 1 to 5 c.cm. of 7 per cent. solution. *Dose.*—1.5 to 5 mls. until a total of 40 to 45 mls. has been given.

Gelsemium. *Gelsemium radix* has been used as febrifuge, anti-spasmodic and analgesic. It has also been used in acute and chronic neuralgia, toothache, uterine and ovarian pain and chorea. *Dose*—5 to 15 gr.

Gentian violet. The product used therapeutically is purified methyl violet and consists of a mixture of the hydrochlorides of hexa- and pentamethyl pararosaniline with some tetramethyl-pararosaniline hydrochloride. The drug is employed intravenously in septicæmia and endocarditis. It has also been tried in encephalitis. The dye is stated to be specific for Gram-positive group of organisms only. For direct application a solution, 1 in 500 or 1 in 1000, has been recommended. *Dose.*—0.007 gm. per kilo intravenously in a $\frac{1}{4}$ to 1 per cent. aqueous solution. It is also used for intestinal parasites in doses of 1 to 3 gr. by the mouth.

Haliverol. It is a combination of halibut-liver oil with irradiated ergosterol, and is stated to be 60 times as potent in vitamin A, and 250 times as potent in vitamin D as cod-liver oil. Haliverol is darker in colour than cod-liver oil, and has a slightly fishy, but not unpleasant taste. The dose is so small that no difficulty is experienced in administration. It is recommended for the treatment of rickets, malnutrition and tetany in children, and for adults during pregnancy, lactation, and at times of lowered resistance to respiratory infections. Three drops of haliverol is equivalent to one teaspoonful of cod-liver oil. Infants and children can be given up to 30 drops daily. A dose of 10 to 15 drops three times a day is suitable for adults.

Helmitol. It is an anhydro-methylene citrate of hexa-methylene-tetramine. It is employed in similar doses to its parent substance, urotropine as a urinary antiseptic, and acts by the liberation of formaldehyde.

Haliverol. It is a concentrated sterile solution of the anti-anæmic factor of the mammalian liver, prepared for intramuscular injection in the treatment of pernicious anæmia. An initial dose of 4 c.cm. should be given followed by 2 c.cm. daily for 3 or 4 days. A normal blood count is usually obtained after the administration of 10 to 12 c.cm. and can be maintained by doses of 2 c.cm. at intervals of 2 to 6 weeks.

Hepol. It is a concentrated tasteless preparation containing the active principle of liver supplied in the form of capsules, powder and liquid, and also as a sterilised solution for intramuscular injections. The capsules are equivalent to $\frac{1}{4}$ oz. and 1 oz. of fresh liver. Hepol in sterilised solution is supplied in 2 c.cm. and 5 c.cm. ampoules containing the active principle of 40 and 100 gm. of liver but has the

therapeutic activity of at least 1000 gm. taken by mouth. For intravenous injection, the solution may be diluted with four parts of normal saline, and the solution warmed to blood heat before injection. Intravenous injections should be made slowly at not more than 2 c.cm. per minute.

Histamine. It can be injected hypodermically in doses of one mgm. (1/64 gr.), and this is not toxic to man. Its general action is vagotropic and more pronounced in the vagotonics.

Histidine (Larostidin). It consists of a sterile, isotonic 4 per cent. solution of histidine monohydrochloride and is a new and highly successful method of dealing with gastric, duodenal and jejunal ulcers. It is given as subcutaneous or intramuscular injection in doses of 5 c.cm. Treatment consists in the daily administration of one larostidin ampoule for about three weeks. No other therapy is necessary after this. After 4 or 5 larostidin injections pain disappears and nausea, vomiting, hyperacidity, etc., are relieved. After ten days a normal diet may be resumed. Important features of the larostidin treatment are its comparatively moderate cost and its avoidance of special ulcer diet, prolonged rest treatment and operative measures.

Hexylresorcinol (Caprokol, dihydroxy-4-hexyl benzol). It is a stable compound forming white crystals. It is a powerful germicide and the power is retained in both acid and alkaline urine even in high dilution. Given by mouth, the compound is secreted in the urine at a rate producing continuous action in the urinary tract. Early cases of Bact. coli and Staphylococcal infections of the urinary tract have been successfully treated with the drug. It is of value in disinfection of wounds draining the urinary tract. The anthelmintic effect of the drug in hookworm, trichina and ascaris infections, has been stated to be good. *Dose.*—2 to 10 gr. thrice daily. Gelatin capsules containing 0.15 gm. in 25 per cent. olive oil solution are taken immediately after each meal thrice daily, three to four being taken on each occasion.

Hydnocarpus oil (Oleum hydnocarpi, B. P. 1932). It is a fatty oil obtained by cold expression from the seeds of *Hydnocarpus wightiana*, an Indian tree of the same natural order as *chaulmoogra*, to which it is now preferred. *Dose.*—5 to 15 min. gradually increased to 60 min. by subcutaneous or intramuscular injection, 30 min. gradually increased to 75 min. (See page 917).

Ethyl esters of hydnocarpus oil (Oleum hydnocarpi æthylicum, B. P. 1932). It consists mainly of the ethyl esters of *chaulmoogric* and *hydnocarpic* acids, and is prepared by esterification of the fatty acids of *hydnocarpus* oil with ethyl alcohol. *Dose.*—1 c.cm. intramuscularly.

Sodium hydnocarpate. The sodium salt of the low melting-point fatty acid of *hydnocarpus* oil. *Dose.*—10 c.cm. of a 1 per cent. solution. (See page 926).

Icoral. It is used as a combined circulatory and respiratory stimulant in infectious diseases, after operations, in cases of poisoning, asphyxia of the new-born, and prophylactically before lumbar anæsthesia. The normal dose is 2 c.cm. of the 5 per cent. solution to be injected intramuscularly, 2 to 4 c.cm. subcutaneously, or 0.5 to 1 c.cm. intravenously (injected slowly). In children, 1 c.cm. of the 0.5 per cent. solution is given.

Iodized oil. It is indicated in bronchiectasis, chronic bronchitis, atelectasis of the lung, bronchial asthma, acute laryngitis and tracheitis. It is definitely contraindicated in acute tuberculosis and acute abscess of the lung. The oil is introduced into the tracheo-bronchial tree after the pharynx, larynx and upper portion of the trachea have been sprayed with 1 per cent. cocaine solution. Warmed iodized oil is dropped directly into the trachea from a 10 c.cm. syringe with attached laryngeal canula. An initial installation of 5 to 10 c.cm. may be given but usually 10 to 20 c.cm. can be given at the first treatment. This is repeated daily for several days.

Isphagula (*Plantago ovata*). See page 416

Kalzana. It is calcium-sodium-lactate, and is given in larger doses than those of 15 gr. and is recommended as a popular preparation for oral calcium administration. It has no advantage over calcium lactate.

Kurchi (*Holarrhena anti dysenterica*). See page 398.

Krysolgan. It is the sodium salt of p-amino-o-aurophenol carbonic acid. It was introduced by Feldt in 1917 for the treatment of tuberculosis. After an extended trial it proved of little use and has been replaced entirely for this purpose by sanocrysin. Krysolgan was also used in the treatment of lupus erythematosus and here proved to have of distinct value. Schamberg has recently shown that sanocrysin is even more effective, and in some cases eruptions of long-standing disappear rapidly after two or three injections. Prolonged and careful treatment may be necessary, however, and some patients are completely resistant to gold treatment. The drug is given intravenously and the initial dose should be from 0.01 to 0.025 gm. (1/6 to 3/8 gr.) dissolved in 5 c.cm. of sterile distilled water. Subsequent doses at weekly intervals are increased by 0.01 gm., with a maximum dose of 0.075 to 0.1 gm. If reactions such as fever, rigors, vomiting, diarrhoea, stomatitis, albuminuria, rashes, or signs of shock occur subsequent doses should be smaller and only continued after the reaction has subsided completely. In the event of a severe reaction the drug must be discontinued. Cases of the disseminated type of lupus erythematosus often show extreme idiosyncrasy to gold salts, and if used at all here, the dose should not exceed 0.005 gm. to begin with, and the maximum dose should not be greater than 0.025 gm.

Leeches. Two varieties of leech are in common use. *Hirudo medicinalis*, the speckled leech, which has six stripes and a yellow spotted belly; and *Hirudo quinquestrata*, the Australian leech, which has five stripes and a spotless yellow belly. Leeches provide a valuable means of counter-irritation, and are particularly useful for the relief of pleuritic or pericardial pain. In the early stages of lobar pneumonia, for instance, half-a-dozen leeches applied to the affected side will frequently secure quick relief. Again, for the pain associated with the engorged liver of heart failure the application of a few leeches often brings relief. They should be applied when possible over areas where gentle pressure will readily arrest any excessive hæmorrhage from the bites, and in applying them they should not be touched by the fingers, but simply inverted on to the skin from a small wooden box. The part should be clean and free from soap or antiseptics and if the

leech refuses to bite, a small scratch with a needle on the skin will readily overcome the difficulty. They should be allowed to drop off in the ordinary way, but if required to be removed a little salt sprinkled over their backs acts as a brisk emetic and they drop off at once. A healthy leech will usually abstract about 2 dr. of blood, and if further bleeding from the bites is required a hot fomentation may be applied or the part may be cupped. Excessive bleeding from leech bites is rare, but if it occurs, pressure and the application of a little adrenalin solution on gauze will arrest it.

Lipiodol. It is an iodised poppy-seed oil containing 40 per cent. of iodine (0.54 gm. per c.cm.). It has an amber colour and faint garlic odour and is practically tasteless. The high content of iodine renders it opaque to X-rays, and it is now used extensively in radiological diagnosis following the pioneer work of Sicard and Forestier in Paris. In the diagnosis of bronchial obstruction or of bronchiectasis a radiograph taken after the introduction of lipiodol into the bronchial tree is frequently indispensable. The oil is introduced under local anaesthesia either by a laryngeal catheter or by a syringe and stout needle through the crico-thyroid membrane. About 20 c.cm. are sufficient to outline the bronchial tree on one side in an adult. For children 5 to 10 c.cm. may be used. It is also used in the radiological survey of bronchial or pleural fistula, urethral strictures, and spinal tumours. For the latter two special varieties of lipiodol are used, *lipiodol radiologique ascendant* containing 10 per cent. of iodine, and *lipiodol radiologique descendant* containing 85 per cent. of iodine. The former is introduced into the subarachnoid space by lumbar puncture in quantities of 1 or 2 c.cm. after withdrawal of a few c.cm. of cerebro-spinal fluid.

Lobeline. It is the alkaloid obtained from *Lobelia inflata* and has a powerful stimulant action upon the respiratory centre, lowering the threshold to carbon dioxide. It has been tried clinically in respiratory failure during anaesthesia, but its effects are uncertain. In morphine poisoning and asphyxia neonatorum it has been used with success. *Dose.*—for adults $\frac{1}{2}$ gr. hypodermically, and for children $\frac{1}{20}$ gr.

Marmites. See page 200.

Mercurochrome-220 soluble. See page 747.

Myocrisine (Sodium aurothiomalate). It is a pale yellow powder, containing 50 per cent. of gold. Myocrisine is supplied in aqueous solution and in oil suspension for intramuscular injections in the treatment of pulmonary tuberculosis, rheumatoid arthritis and lupus erythematosus. Myocrisine injections are practically painless, and give rise to no local reactions. The aqueous solution can be given by subcutaneous injections. The ampoules are supplied singly or in boxes of ten in doses of 0.01, 0.05, 0.10, 0.20, 0.3 and 0.5 gm. The injections are given weekly, the dose being gradually increased until an average total dosage of 2 gm. has been given. The course may be repeated after an interval of one month or six weeks.

Methylene blue. The drug is analgesic and is of service in rheumatism and painful nervous affections. It has also been used in malaria, nephritis and retinitis. The usual dose of the drug is 1 to 4 gr. given in pill, cachet or capsule. A dose of 1 gr. has been used hypodermically.

The drug has also been used in 2 dr. doses thrice daily in actinomycosis. It has also been used in other affections such as black water fever, ulcerative colitis (irrigation with 1 in 1,000 solution), cystitis (2 per cent. solution), dysentery (rectal injection with 1 in 5,000), chronic suppurative otitis media and conjunctivitis (1 in 500), intertriginous eczemas (3 to 5 per cent. solution) and purulent discharges from the eye socket (0.1 per cent. solution).

Neostibosan. See page 444

Neptal. It is the mercury salt of salicylaminoacetic acid, and is now used as an alternative to novasurol or salyrgan for the production of diuresis in cardiac cedema. It has the advantage that it may be given by intramuscular injection without local irritation. It is a powerful diuretic in congestive heart failure, and the response is within a few hours, and continues for 48 hours. It is given as a 10 per cent. solution in doses of 1 or 2 c.cm. intravenously or intramuscularly and may be repeated, if necessary, after a few days.

Neotropin. It is a dye of the azo-pyridin series, possessing a marked power of penetration and tissue affinity and is bactericidal even in a dilution of 1 in 520,000, 2 or 3 hours after administration, its presence can be observed by the yellowish red colour of the urine. Neotropin is recommended for the treatment of all bacterial infections of the bladder and kidneys. Its antiseptic properties are not dependent on the reaction of the urine. It is also claimed to have a sedative effect on the acute inflammatory symptoms. Neotropin is supplied in dragees of 0.1 gm. (1.5 gr.) and the dose is 4 to 6 dragees daily after meals. In prolonged treatment an interval of two or three days is advisable after every 5 days treatment.

Novalgin (sodium phenyl-dimethylpyrazolone methyl-amino-methane-sulphonate). It is claimed to be an anti-rheumatic, suitable for the treatment of articular and muscular rheumatism and better tolerated than salicylates. *Dose.*— $7\frac{1}{2}$ to 15 gr. three times daily for adults, and proportionately less for children.

Novasurol. It is the sodium salt of oxy-mercuri-o-chlorophenoxy-acetate of diethyl-barbituric acid, and contains 33.9 per cent. of mercury in a non-ionisable form. It is used as a neutral sterile 10 per cent. solution in doses of 1 c.cm. by intravenous and intramuscular injections. (See page 750).

Novatophan. It is the ethyl ester of methyl-cinchophen, and has been introduced as a substitute for atophan in the treatment of gout and as an alternative to salicylates in the rheumatic diseases. It is a pale yellow crystalline powder without odour or taste, and is nearly insoluble in water and dilute alkalies. Like atophan the drug greatly increases the excretion of uric acid by lowering the renal threshold for this substance. *Dose.*—0.5 gm. or 8 gr.

Nuclein or nucleol. It is a principle of varying and complex composition always containing phosphorus and generally sulphur obtainable from yeast, spleen, liver, milk, yolk of egg, etc. The nuclein from yeast which is chiefly nucleinic or nucleic acid or its soda salt is the one most frequently employed. When nuclein is administered by the mouth or hypodermically, a great increase in the white corpuscles rapidly follows

and the blood serum is found to be strongly toxic to most microbes. Yeast nuclein is soluble in alkaline solutions, it may be given in doses of 10 gr. in water six times a day, or in doses of $\frac{1}{2}$ gr. hypodermically, much larger doses have been given. Mourek's hypodermic solution is made by dissolving $7\frac{1}{2}$ gr. of splenic nuclein in as much as 5 per cent. soda solution as will cause it to dissolve; $7\frac{1}{2}$ gr. carbolic acid are added, and water to 26 dr. Of this $\frac{1}{2}$ to 2 dr. may be injected. A solution of yeast nuclein, of 5 per cent. strength is obtainable, the dose of which is 1 dr.

Omnopon or pantopon. It is a brown powder containing the hydrochlorides of all the twenty alkaloids of opium, half of its weight consisting of morphia. It is said to have less action on the respiratory centre than morphia and it is recommended hypodermically in twilight anæsthesia in 15 min. doses of a 2 per cent. solution; $\frac{1}{6}$ to $\frac{1}{3}$ gr. hypodermically has been given as a hypnotic in mania.

Opocalcium. It is a combination of parathyroid, suprarenal and thymus glands, with the phosphate, glycerophosphate, fluoride, and carbonate of calcium, magnesium phosphate, and manganese nucleinate. It is recommended for the remineralisation of the body in tuberculosis, pregnancy, fractures, etc. Opocalcium associated with irradiated ergosterol is known as irradiated opocalcium. *Dose.*—for adult, six tablets or three dessertspoonfuls of the granules daily, children under ten years should receive half the adult dose.

Ostellin. It is the unsaponifiable fraction of cod-liver oil and contains the active medicinal properties of the oil concentrated 2,000 times. For convenience of administration this extract is suspended in glycerine so that 4 min. are equivalent to 1 dr. of the original oil. It affords a convenient means of giving large doses of vitamins A and D and at the same time avoiding the fatty constituents of codliver oil which are rather apt to cause nausea and digestive disturbances.

Pandigal. See page 248.

Papain or papayotin. It is a ferment prepared from the juice of the unripe fruit of *Carica papaya* in the form of a white powder. It possesses the power of digesting animal substances; 1 dr. will peptonise 200 gr. pressed blood fibrin. Papayotin is, strictly speaking, the milky juice obtained by incisions made into the unripe fruit collected and dried. The words *papain and papayotin are, however, now used synonymously. The ferment will act in an acid, neutral, or alkaline medium which gives it advantages over pepsin. Moreover, the action of papain continues all down the intestines, whilst that of pepsin ceases in contact with the alkaline juices. Its activity is variable, however, and always much less than that of pepsin. There is no other combination which will give so good results in many gastric affections as, papain 3 gr., sodii bicarb. 30 gr., mag. carb. pond. 20 gr., bism. carb 10 gr., morphine hydrochlor. $\frac{1}{18}$ gr. The drug can be given in tablets, with or without soda, and as glycerinum papain of any strength.

* **Para-thormone** (Lilly). It is a stable, aqueous solution containing the active substance of the parathyroid glands of cattle, and is prepared by the method of acid extraction developed by Collip. The extract is standardised by the increase in blood-serum calcium which follows

an injection; 1 unit is defined as 1/100 of the amount required to cause an increase of 5 mgm. in the blood-serum calcium of a 20 kg. dog fifteen hours after injection. The extract is supplied in 5 c.cm. ampoules containing 100 units. To prevent the recurrence of tetany doses ranging from 10 to 25 units daily are usually sufficient. In infants 10 to 20 units daily are advocated. The effect of a single dose reaches its peak in 12 to 18 hours, and continues for 24 to 36 hours. One injection daily or every other day is usually sufficient in chronic tetany.

Peptone. This is a white powder, being the proteins and albuminoids prepared by peptonising meat. Many varieties of peptonised beef, wheat, and milk preparations are available as foodstuffs in dyspepsia. Peptone can be used to produce desensitisation to protein substances and it has been used in the treatment of allergic diseases such as asthma, hay fever, urticaria, Quincke's oedema, eczema and certain diarrhoeal affections; 5 gr. are given, dissolved in 5 c.cm. saline solution, the dose being increased to 15 gr. in the third week. Umber has used a sterile 5 per cent. solution of the alcohol soluble fraction of peptone (Witte) with the addition of 1 per cent. novocaine. This solution he injected in quantities of 5 to 10 c.cm. subcutaneously on three successive days. Schiff used a 33 per cent. solution prepared by mixing water and glycerine to Armour's dry peptone, ensuring solution by friction and gentle heating. The preparation was then filtered and sterilised; 3 min. is a safe initial dose, and this was increased by 1 min. at biweekly or triweekly intervals up to 1 c.cm. He claimed that relief followed such treatment in a considerable number of asthmatic patients, and other writers have established that such treatment has a place in the management of asthma when a definite allergic factor can be shown to be present.

Phanodorm (Cyclohexenyl ethyl-barbituric acid). It is a white powder with bitter taste, and resembles veronal in its actions, but is excreted more rapidly so that its action is not so lasting. It is mainly used as a sedative in nervous insomnia, neurasthenia, and psychoses, in doses of $1\frac{1}{2}$ gr. up to 6 gr.

Phenolphthalein dyes. A number of derivatives of phenolphthalein in which bromine or iodine is combined in the molecule have recently been introduced for testing kidney and liver functions. All of them are excreted in the urine and bile and may be estimated colorimetrically in the former or in the case of the biliary tract their presence may be shown by their opacity to X-rays. Sodium phenoltetraiodophthalein contains about 58 per cent. iodine, and following intravenous injection in doses up to 2.5 gm. as an 8 per cent. solution or administered by the mouth in doses up to 4 gm. in capsules it appears in the normal gall-bladder in sufficient concentration to produce a well-defined shadow on X-ray examination. It is usually given overnight and the stomach is kept empty till the following morning, when a small meal of cream or other fat is given and the radiograms are then taken at intervals. In order to use the dye for the determination of liver function, the amount present in the blood serum is determined $\frac{1}{2}$ hour and 1 hour after the intravenous injection by comparison with standard solutions. Sodium tetrabromophenolphthalein contains about 47 per cent. of bromine and sodium tetraiodophenolphthalein contains not less than 58 per cent.

of iodine both are used to visualise the gall bladder by X-ray examination. The former is given intravenously in doses of 0.1 gm. per kilo, 4 to 5 gm. dissolved in about 40 c.cm. of freshly distilled water being used for an adult. Sodium tetraiodophenolphthalein may be given in this way in smaller doses up to 8 gm., but is more usually administered orally in doses up to 4 gm. in capsules.

Plasmoquine. See page 590.

Protargol (Silver protein or novargin). It is a compound of silver and albumose,* and contains 8 per cent. silver. It is a powerful anti-septic, is very soluble and highly penetrating, and is not precipitated by albumin, and is practically non-irritating. It is a very efficacious remedy for gonorrhoea when injected in $\frac{1}{2}$ per cent. solution three times a day, increased to 2 per cent. A 20 per cent. solution is used as a prophylactic against gonorrhoea. It is extensively used in eye surgery.

Pyridium. It is an azo dye containing 28 per cent. nitrogen. When given by mouth it is absorbed readily, is non-toxic, and non-irritant, and is rapidly excreted through the urinary tract where it has a bactericidal action against staphylococci, streptococci, gonococci, and Bact. coli. It is usually given by mouth in doses of 3 gr. thrice daily in capsules or as tablets; 0.3 per cent. solution is used for urethral injection, which must be prepared with distilled water, as the salts present in tap water may precipitate the free base from the solution.

Radiostol. Radiostol, in the form of pellets or solution in arachis oil, is standardised in terms of the international standard, which contains 1,000 units of vitamin D activity per c.cm. The usual dose for the treatment of rickets, tetany, etc., is two or three pellets or 30 drops of the solution daily. *Radiostoleum* is a similar preparation containing a concentrate of vitamin A added to radiostol. It may be given as the oily solution in doses of 10 to 20 drops daily, or in capsules 1 to 3 daily.

Radio-malt. It is a combination of radiostoleum with measured concentrates of vitamins B₁ and B₂, and is given in doses of 1 to 4 dr. two or three times daily. *Viosterol* is a similar preparation to radiostol, and contains 10,000 units of vitamin D each c.cm., the daily curative dose for rickets should not be less than 2 c.cm. *Adexolin* is a preparation containing both vitamins A and D; each capsule contains 150 units of vitamin A and 1,000 units of vitamin D, three or more may be given daily as required.

Radium. See page 136.

Salyrgan. See page 751.

Scarlet red. It is a compound of beta-naphthol, diazotised amino-azo-o-toluol, and *scarlet red sulphonate*, which has a marked power of stimulating the growth of epithelial cells, and is used in the treatment of chronic ulcers, wounds and burns in the form of an ointment containing from 4 to 8 per cent. of the dyes.

Soamin. See page 661.

Sodium morrhuate. It is the sodium salt of a fatty acid obtained by the saponification of cod-liver oil. It has recently come into use as a 5 or 10 per cent. solution for the treatment of varicose veins by injection. It has the advantage over quinine solutions that it is non-toxic, and over salicylates that it produces little pain or local inflammatory reaction. From 1 to 5 c.cm. of the 5 per cent. solution is

usually sufficient for a single injection and several veins may be treated at one sitting. Injections should be made with a fine needle from above downwards, and the patient should be standing, so that the veins are full. They should be spaced at intervals of $1\frac{1}{2}$ to 2 inches along the length of vein to be sclerosed. The effect is rapid, thrombosis occurring in the injected veins immediately.

Sodium thiosulphate. See page 694.

Solganal. See page 966.

Somnifaine (liquid hypnotic). It is an alcohol-glycerin-water solution of diethyl and allyl-isopropyl-barbiturates of diethylamine. One c.cm. is equivalent to 0.1 gm. of diethylbarbituric acid and 0.1 gm. of allylisopropyl barbituric acid. Somnifaine is recommended as a powerful hypnotic and sedative. It can be administered by intramuscular or intravenous injection, as well as orally.

Stovarsol. See page 409 and 668.

Sulfosin. It is a suspension of sulphur in olive oil, and is used for non-specific therapy by intramuscular injection. It is given as a course of injections, usually commencing with $\frac{1}{2}$ c.cm. or 1 c.cm. and gradually increasing the doses up to 5 c.cm. Sulfosin has been used in the treatment of bronchial asthma, rheumatoid arthritis, disseminated sclerosis, and various syphilitic affections of the nervous system, particularly general paralysis of the insane.

Taka-diastase. It is a yellowish-white powder, being a ferment produced by cultivating a fungus (*Eurotium oryzae*) on heated rice or bran. It changes in a few minutes 100 times its weight of starch into maltose. 2 to 5 gr. may be given in water, in the dyspepsia caused by starchy foods in cases of hyperacidity of the stomach. It is in this latter condition that the best results of the drug are observed, and it may be prescribed like papain with sodium bicarbonate.

Tannafax. A tannic acid jelly for use in treatment of burns. It is prepared with a water-soluble antiseptic base, it can be easily bathed off when removal of dead tissue is called for.

Thallium acetate. It has recently been introduced for the treatment of ringworm of the scalp especially in children. The exact dose of thallium acetate employed is usually 8 mgm. per kilo of body weight; this is administered at one time, and a second dose should not be given except after an interval of at least 2 months, as the drug is cumulative and requires 2 to 3 months for excretion by the kidneys. The salt is given by mouth dissolved in water. The hair shows signs of becoming loose within 6 to 8 days, and complete epilation is effected in from 16 to 19 days. The hair grows again after 4 to 6 weeks.

Theobromine. It is an alkaloid obtained from the seeds of *Theobroma cacao*, in white, crystalline powder, resembling caffeine in action when given in 10 gr. doses. Its sodium-salicylate compound (Diuretin) is now official. Theobromine calcium salicylate or calcium diuretin containing 48 per cent. of theobromine is used as an alternative to diuretin.

Thiosarmin. This is the name given to sulpharsphenamine prepared by Brahmachary. The doses are like those of sulpharsphenamine and used in syphilis.

Tryparsamide (Moranyl). It is sodium ²⁴p-phenylglycinamide-p-arsenate, containing 24.6 per cent. of arsenic in pentavalent organic

combination. It is a crystalline powder, freely soluble in water. *Dose* — 1 to 2 gm. weekly, by injections. It is used in neurosyphilis and sleeping sickness.

* **Uroselectan B.** See page 65.

Yatren. See page 405.

Yeast. It is rich in nucleic acid and in vitamin B., is given in doses of a tablespoonful in beriberi and infections such as recurring boils. Levurine is a brown powder prepared by dehydrating yeast, and is given in 1 dr. doses. •

DILUTION TABLES

(Metric System)

(Per 1 c.cm. solution)

1 in 100	10.0 mg.	1 in 600	1.66 mg.
1 in 200	5.0 mg.	1 in 700	1.43 mg.
1 in 300	3.33 mg.	1 in 800	1.25 mg.
1 in 400	2.5 mg.	1 in 900	1.11 mg.
1 in 500	2.0 mg.	1 in 1,000	1.0 mg.

(Imperial System)

Quantity of Medicament (in grains) required for making

Percent- age	1 fluid drachm	1 fluid ounce	1 pint	Parts
1	0.547	4.875	87.5	1 in 100
2	1.094	8.750	175.0	1 in 50
3	1.640	13.125	262.5	1 in 33.33
4	2.187	17.500	350.0	1 in 25
5	2.734	21.875	437.5	1 in 20
6	3.281	26.250	525.0	1 in 16.66
7	3.828	30.625	612.5	1 in 14.28
8	4.375	35.000	700.0	1 in 12.5
9	4.922	39.375	787.5	1 in 11.11
10	5.468	43.750	875.0	1 in 10

STRENGTHS OF SALINE SOLUTIONS

NORMAL SALINE. Sodium chloride 90 gr., water 1 pint.

HYPERTONIC SALINE. Sodium chloride 120 gr., water 1 pint.

HYPOTONIC SALINE. Sodium chloride 60 gr., water 1 pint.

ALKALINE ISOTONIC SOLUTION. Sodium chloride 90 gr., sodium bicarbonate 60 to 120 gr., water 1 pint.

NORMAL SALINE WITH GLUCOSE. Sodium chloride 90 gr., glucose 1 oz., water 1 pint.

ROGER'S HYPERTONIC SALINE. Sodium chloride 120 gr., calcium chloride 4 gr., water 1 pint.

Weights and Measures

METRIC SYSTEM

The multiples in the Metric System are denoted by the Greek prefixes: *deka*=10; *hecto*=100, *kilo*=1,000, *myria*=10,000, the sub-divisions by the Latin prefixes: *deci*= $\frac{1}{10}$, *centi*= $\frac{1}{100}$; *milli*= $\frac{1}{1000}$.

Measures of Length

1 Kilometre	Km.	= 1000'0 M.
1 Metre	M.	= 1'0 M.
1 Centimetre	cm.	= 0'01 M.
1 Millimetre	mm.	= 0'001 M.
1 Micron	μ .	= 0'001 mm.
1 Micromillimetre	$\mu\mu$.	= 0'000001 mm.

Measures of Mass (Weight)

1 Kilogram	Kgm.	= 1000'0 Gm.
1 Gramme	Gm.	= 1'0 Gm.
1 Centigram	cgm.	= 0'01 Gm.
1 Milligram	mgm.	= 0'001 Gm.

Measures of Capacity

1 Hectolitre	Hl.	= 100'0 L.
1 Litre	L.	= 1'0 L.
1 Centilitre	cl.	= 0'01 L.
1 Millilitre	mil.	= 0'001 L.
1 Decimil	dml.	= 0'0001 L.
1 Centimil	cml.	= 0'00001 L.

Cubic centimetre (c.c.m.). For practical purposes the cubic centimetre is generally used in the measurement of fluids and is regarded as equivalent to the millilitre (mil.) (1 mil. = 1'000028 c.c.m. approximately).

Drop. It is defined as the drop from a tube, which at 15°C. delivers 20 drops of distilled water to the gramme.

Indian Domestic Measures of Mass

1 Tola	= Wt. of a Rupee (180 Gr.)
1 Chhatak	= 4 Kanchas (5 Tolas)
1 Pown	= 4 Chhataks
1 Seer	= 16 Chhataks 80 (Tolas)
1 Maund	= 40 Seers

The maund and seers used locally in different parts of India are not the same. The above measure used in Bengal are used by all the Railways and Steam Navigation Companies, etc., throughout India.

IMPERIAL SYSTEM

Measures of Mass (Weight)

AVOIRDUPOIS WEIGHT

[Used for measuring all ordinary goods]

1 Ounce (oz.)	= 16 Drachms (dr.)
1 Pound (lb.)	= 16 Ounces
1 Stone (st.)	= 14 Pounds
1 Quarter (qr.)	= 2 Stones
1 Hundredweight (cwt.)	= 4 Quarters
1 Ton	= 20 Hundredweight

TROY WEIGHT

[Used for weighing gold, silver and precious stones]

1 Pennyweight (dwt.)	= 24 Grains (gr.)
1 Ounce (oz.)	= 20 Pennyweights
1 Pound (lb.)	= 12 Ounces
1 Pound Troy = 5,760 grains	
1 Pound Avoir = 7,000 grains.	

APOTHECARIES' WEIGHT

[Now used by apothecaries for retail sale only.]

1 Scruple (scr.)	= 20 Grains (gr.)
1 Drachm (dr.)	= 8 Scruples
1 Ounce (oz.)	= 8 Drachms
1 Pound (lb.)	= 12 Ounces (5,760 gr.)

The 'Grain' has the same weight throughout.

MEASURES OF CAPACITY

1 Fl. Drachm (fl. dr.)	= 60 Minims (min.)
1 Fl. Ounce (fl. oz.)	= 8 Fl. Drachms
1 Pint (pt.)	= 20 Fl. Ounces
1 Gallon (gal.)	= 8 Pints

One 'Minim' is the volume at 62°F. of 0'9114583 grain of water.

English Domestic Measures

1 Teaspoonful	= 1 fluid dr.
1 Dessertspoonful	= 2 fluid dr.
1 Tablespoonful	= 4 fluid dr. (1 oz.)
1 Wineglassful	= 2 fluid oz.
1 Teacupful	= 5 fluid oz.
1 Tumblerful	= 8 fluid oz.
1 Quart	= 32 fluid oz.

CONVERSION OF MEASURES

LENGTH—

1 Kilometre	= 0.6214 mile
	= 1093.6 yards
1 Metre	= 39.3701 inches
	= 3.2809 feet
	= 1.0936 yards
1 Centimetre	= 0.3937 inch
1 Millimetre	= 0.0394 inch
1 Inch	= 2.54 centimetres
1 Foot	= 30.48 centimetres
1 Yard	= 0.9144 metre
1 Mile	= 1.6093 kilometres

CAPACITY—

1 Litre	= 1.7598 pints
	= 0.2203 gallon
	= 0.0858 cubic foot
	= 35.196 fl. oz.
1 c.cm. (mil.)	= 16.89 minims
	= 0.28152 fl. dr.
	= 0.03519 fl. oz.
1 Minim	= 0.0592 c.cm.
1 Pint	= 0.5683 litre
1 Fl. Ounce	= 28.416 c.cm.
1 Fl. Drachm	= 3.552 c.cm.
1 Cubic Foot	= 28.38 litres
	= 6.225 gallons
1 Cubic Inch	= 16.386 c.cm.
1 Cubic Metre	= 35.316 cubic feet
1 Gallon	= 4.54596 litres
	= 0.16037 cubic foot
	(Vol. of 10 lb. water at 62° F.)
1 Eng. Gallon	= 1.2 U.S.A. Gallons
1 U.S.A. Gallon	= 0.833 Eng. Gallon

MASS (Weight)--

1 Kilogram	= 2.2046 pounds (Av.)
	= 85.27 ounces
	= 1.0715 seers
1 Gramme	= 15.48296 grains
	= 0.03527 ounce
1 Milligram	= 0.01548 grain
1 Grain	= 0.0648 gramme
	= 0.00228 ounce
1 Ounce (Av.)	= 28.3495 grammes
	= 437.5 grains
	= 2.4803 tolas
1 Ounce (Tr.)	= 31.104 grammes
	= 460 grains
	= 2.6666 tolas
1 Pound (Av.)	= 453.592 grammes
	= 7,000 grains
	= 0.4861 seer
1 Pound (Tr.)	= 373.25 grammes
	= 5,760 grains
	= 0.4 seer
1 Stone	= 6.85029 kilogram
	= 6.804 seers
1 Hundredweight	= lmd. 14sr. 7½ch.
1 Ton (Av.)	= 27.2 maunds
1 Tonne (Metric)	= 0.984 ton (Av.)
1 Maund	= 82.3 pounds (Av.)
	= 100 pounds (Tr.)
1 Seer	= 80 tolas
	= 0.9831 kilo.
	= 2.0571 pounds (Av.)
	= 2.5 pounds (Tr.)
1 Chattak	= 5 tolas (2 fl. oz.)
1 Tola	= 180 grains
	= 11.664 grammes

Weights of Indian Coins

1 Gold Sovereign	= 123 grains
1 Silver Rupee	= 180 grains
1 Silver 8-anna bit	= 90 grains
1 Silver 4-anna bit	= 45 grains
1 Silver 2-anna bit	= 22.5 grains
1 Nickel 4-anna bit	= 104 grains
1 Nickel 2-anna bit	= 88 grains
1 Nickel 1-anna bit	= 60 grains
1 Copper pice	= 76 grains
1 Copper half-pice	= 88 grains
1 Copper pie (½ pice)	= 25 grains

Arithmetical Memoranda

Ratio of circumference of a circle to diameter	= π = 3.14159 or $\frac{22}{7}$
Circumference of a Circle	= $2\pi r$
Area of a Circle	= πr^2
Surface of a Sphere	= $4\pi r^2$
Volume of a Sphere	= $\frac{4}{3}\pi r^3$
Volume of a Cone	= $\frac{\pi r^2 h}{3}$

WEIGHTS AND MEASURES USED IN DIFFERENT COUNTRIES AND FOREIGN CURRENCY

The Value given is that at par. Current quotations can be obtained from the daily newspapers

Country	Weights and Measures	Money
Argentina	Metric system	100 centavos=1 peso (gold)=4s. app.
Austria	Metric system	100 groschen=1 Aust. schilling=7d. app.
Belgium	Metric system	100 centimes=1 Fc. 5 Fcs.=1 Belga =7d. app.
Brazil	Metric system	1,000 reis=1 milrei=2s. 8d.
Bulgaria	Metric system	100 stotinki=1 leva=1/4d. app.
Canada and Newfoundland	As Gt. Britain, except 1 cwt. = 100 lb. 1 ton=2,000 lb.	100 cents=1 dollar =4s. 2d. app.
Ceylon	1 maund=40 seers=82 lb. app. Also as Gt. Britain,	100 cents=1 rupee=1s. 6d.
Chile	Metric system	100 centavos=1 peso=6d. app.
China	1 picul = 100 catties = 133 1/2 lb. 1 chang = 141 ins.	Silver Standard. Currency conditions are chaotic at present
Czecho-Slovakia	Metric system	100 heller = 1 krone=1.40d. app.
Denmark	Metric system	100 ore=1 krone=1s. 1 1/2d. app.
Norway, Sweden		
Egypt and Sudan	1 okieh = 1'3206 oz. 1 rotl = '8904 lb. 1 oke = 2'7513 lb. 1 cantar=99'0492 lb. 1 ardeb =43.55 galls.	10 millimes=1 piastre. 100 piastres =£1/6=£1. 0s. 6 1/2d. app.
France	Metric system	100 centimes=1 franc=1.98d. app.
Germany	Metric system	100 pfennigs=1 Reichsmark=11 1/2d.
Greece	1 oke =2'8 lb. 1 dramion=111 oz. 1 oke of capacity=2'34 pints	100 lepta=1 drachma=1/2d. app.
Holland	Metric system	100 cents=1 gulden=1s. 8d. app.
Hong Kong	As Gt. Britain	100 cents=1 dollar=2s. 1d.
India	1 maund = 40 seers = 82 lb. app. Also as Gt. Britain	4 pice=1 anna. 16 annas=1 rupee=1s. 6d. 100,000 rupees=1 lakh
Italy	Metric system	100 centesimi=1 lire=2 1/2d. app.
Japan	1 kin=1'322 lb. avoird.	10 rin = 1 sen. 100 sen=1 yen = 2s. 0 1/2d. app.
Latvia	Metric system	100 santimi=1 lat=2 1/2d.
Lithuania	Metric system	100 centu=1 litas=5d. app.
Poland	Metric system	100 grosz=1 zloty=5 1/2d. app.
Portugal	Metric system	100 centavos=1 escudo=2 1/2d.
Roumania	Metric system	100 bani=1 lei=1/2d. app.
Russia (U.S.S.R.)	40 funts = 1 pund = 36 lb. 3 sarshins=1 sajena=7 ft. 1 vedro=2'706 imp. galls.	100 kopeks = 1 rouble. 10 roubles = 1 chervonetz
Serbs, Croats and Slovenes (Kingdom of)	Metric system	100 paras = 1 dinar=8 1/2d. app.
Spain	Metric system	100 centimos=1 peseta=9 1/2d. app.
Switzerland	Metric system	100 centimes=1 franc=9 1/2d. app.
Turkey	Metric system (Used by Customs)	40 paras=1 piastre. 100 piastres=£1=18s.
U. S. A.	As Gt. Britain, except 1 wine gall. =.833 imp. galls. 1 ale gall. =1'0166 imp. galls. Cental =100 lb. Short ton=2,000 lb. Long ton=2,240 lb.	100 cents=1 dollar=4s. 2d.

The following countries use English weights and measures: Australia, British West African Colonies, British West Indies, New Zealand, Union of South Africa.

Thermometric Equivalents

Fahr.	Cent.	Reau.	Fahr.	Cent.	Reau.	Fahr.	Cent.	Reau.
212	100°0	80°0	122	50°0	40°0	32	0	0
210	98°0	79°1	120	48°9	39°1	30	-1°1	-0°9
208	97°8	78°2	118	47°8	38°2	28	-2°2	-1°8
206	96°7	79°3	116	46°7	37°3	26	-3°3	-2°7
204	95°6	76°4	114	45°6	36°4	24	-4°4	-3°6
202	94°4	75°6	112	44°4	35°6	22	-5°6	-4°4
200	98°3	74°7	110	40°3	34°7	20	-6°7	-5°8
198	92°2	73°8	108	42°2	33°8	18	-7°8	-6°2
196	91°1	72°9	106	41°1	32°9	16	-8°9	-7°1
194	90°0	72°0	104	40°0	32°0	14	-10°0	-8°0
192	88°9	71°1	102	38°9	31°1	12	-11°1	-8°9
190	87°8	70°2	100	37°8	30°2	10	-12°2	-9°8
188	86°7	69°3	98	36°7	29°3	8	-13°3	-10°7
186	85°6	68°4	96	35°6	28°4	6	-14°4	-11°6
184	84°4	67°6	94	34°4	27°6	4	-15°6	-12°4
182	83°3	66°7	92	33°3	26°7	2	-16°7	-13°8
180	82°2	65°8	90	32°2	25°8	0	-17°8	-14°2
178	81°1	64°9	88	31°1	24°9	-2	-18°9	-15°1
176	80°0	64°0	86	30°0	24°0	-4	-20°0	-16°0
174	78°9	63°1	84	28°9	23°1	-6	-21°1	-16°9
172	77°8	62°2	82	27°8	22°2	-8	-22°2	-17°8
170	76°7	61°3	80	26°7	21°3	-10	-23°3	-18°7
168	75°6	60°4	78	25°6	20°4	-12	-24°4	-19°6
166	74°4	59°6	76	24°4	19°6	-14	-25°6	-20°4
164	73°3	58°7	74	23°3	18°7	-16	-26°7	-21°3
162	72°2	57°8	72	22°2	17°8	-18	-27°8	-22°2
160	71°1	56°9	70	21°1	16°9	-20	-28°9	-23°1
158	70°0	56°0	68	20°0	16°0	-22	-30°0	-24°0
156	68°9	55°1	66	18°9	15°1	-24	-31°1	-24°9
154	67°8	54°2	64	17°8	14°2	-26	-32°2	-25°8
152	66°7	53°3	62	16°7	13°3	-28	-33°3	-26°7
150	65°6	52°4	60	15°6	12°4	-30	-34°4	-27°6
148	64°4	51°6	58	14°4	11°6	-32	-35°6	-28°4
146	63°3	50°7	56	13°3	10°7	-34	-36°7	-29°3
144	62°2	49°8	54	12°2	9°8	-36	-37°8	-30°2
142	61°1	48°9	52	11°1	8°9	-38	-38°9	-31°1
140	60°0	48°0	50	10°0	8°0	-40	-40°0	-32°0
138	58°9	47°1	48	8°9	7°1	-42	-41°1	-32°9
136	57°8	46°2	46	7°8	6°2	-44	-42°2	-33°8
134	56°7	45°3	44	6°7	5°3	-46	-43°3	-34°7
132	55°6	44°4	42	5°6	4°4	-48	-44°4	-35°6
130	54°4	43°6	40	4°4	3°6	-50	-45°6	-36°4
128	53°3	42°7	38	3°3	2°7	-52	-46°7	-37°3
126	52°2	41°8	36	2°2	1°8	-54	-47°8	-38°2
124	51°1	40°9	34	1°1	0°9	-56	-48°9	-39°1

FAHRENHEIT TO CENTIGRADE.—Subtract 32, multiply by 5, divide by 9.

CENTIGRADE TO FAHRENHEIT.—Multiply by 9, divide by 5, add 32.

FAHRENHEIT TO REAUMUR.—Subtract 2, multiply by 4, divide by 9.

REAUMUR TO FAHRENHEIT.—Multiply by 9, divide by 4, add 32.

CENTIGRADE TO REAUMUR.—Multiply by 4, divide by 5.

REAUMUR TO CENTIGRADE.—Divide by 4, multiply by 5.

HEIGHTS AND WEIGHTS OF MEN, WOMEN AND CHILDREN

MEN

Feet and Inches, with shoes

Age	5'0"	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'0"	6'1"	6'2"	6'3"	6'4"	6'5"
16	109	111	114	117	120	124	128	132	136	140	144	149	154	159	164	169	174	179
18	113	115	118	121	124	128	132	136	140	144	148	153	158	163	168	173	178	183
20	117	119	122	125	128	132	136	140	144	148	152	156	161	166	171	176	181	186
22	119	121	124	127	131	135	139	142	146	150	154	158	163	168	173	178	183	188
24	121	123	126	129	133	137	141	144	148	152	156	160	165	171	177	182	187	192
26	123	125	127	130	134	138	142	146	150	154	158	163	168	174	180	186	191	196
28	125	127	129	132	136	139	143	147	151	155	159	164	170	176	182	188	193	198
30	126	128	130	133	136	140	144	148	152	156	161	166	172	178	184	190	196	201
32	127	129	131	134	137	141	145	149	154	158	163	168	174	180	186	192	198	203
34	128	130	132	135	138	142	146	150	155	160	165	170	176	182	188	194	200	206
36	129	131	133	136	139	143	147	151	156	161	166	171	177	183	190	196	202	208
38	130	132	134	137	140	144	148	152	157	162	167	173	179	185	192	198	204	210
40	131	133	135	138	141	144	148	153	158	163	168	174	180	186	193	200	206	212
42	132	134	136	139	142	146	150	154	159	164	169	175	181	187	194	201	208	214
44	133	135	137	140	143	147	151	155	160	165	170	176	182	188	195	202	209	215
46	134	136	138	141	144	148	152	156	161	166	171	177	183	189	196	203	210	216
48	134	136	138	141	144	148	152	156	161	166	171	177	183	189	197	204	211	217
50	134	136	138	141	144	148	152	156	161	166	171	177	183	190	197	204	211	217
52	135	137	139	142	145	149	153	157	162	167	172	178	184	191	198	205	212	218
54	135	137	139	142	145	149	153	157	162	167	173	178	184	191	198	205	212	219

Allow 1 inch for shoes and 10 pounds for clothes.

WOMEN

Feet and Inches, with shoes

Age	4'8"	4'9"	4'10"	4'11"	5'0"	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'0"
16	102	104	106	108	109	111	114	117	120	124	128	132	136	139	143	148	153
18	104	106	108	110	112	114	117	120	123	126	130	134	138	141	145	150	155
20	106	108	110	112	114	116	119	122	125	128	132	136	140	143	147	151	156
22	107	109	111	113	115	117	120	123	126	129	133	137	141	145	149	153	157
24	109	111	113	115	117	119	121	124	127	130	134	138	142	146	150	154	158
26	110	112	114	116	118	120	122	125	128	131	135	139	143	147	151	155	159
28	111	113	115	117	119	121	123	126	130	133	137	141	145	149	153	156	160
30	112	114	116	118	120	122	124	127	131	134	138	142	146	150	154	157	161
32	113	115	117	119	121	123	125	128	132	136	140	144	148	152	155	158	162
34	115	117	119	121	123	125	127	130	134	138	142	146	150	154	157	160	163
36	116	118	120	122	124	126	128	131	135	139	143	147	151	155	158	161	164
38	117	119	121	123	125	127	130	133	137	141	145	149	153	157	160	163	166
40	119	121	123	125	127	129	132	135	138	142	146	150	154	158	161	164	167
42	120	122	124	126	128	130	133	136	139	143	147	151	155	159	162	166	169
44	122	124	126	128	130	132	135	138	141	145	149	153	157	161	164	168	171
46	123	125	127	129	131	133	136	139	142	146	150	154	158	162	165	169	172
48	124	126	128	130	132	134	137	140	143	147	151	155	160	164	167	171	174
50	125	127	129	131	133	135	138	141	144	148	152	156	161	165	169	173	176
52	125	127	129	131	133	135	138	141	144	148	152	157	162	166	170	174	177
54	125	127	129	131	133	135	138	141	144	148	153	158	163	167	171	174	177

Allow 1½ inches for shoes and 6 pounds for clothes.

The average height and weight, in the majority of Indian Races, is lower than that of Europeans. Buchanan gives the average weight of a Bengali at 109 lb., and Lewis, of a U. P. man, at 110 lb.

Buchanan's formula for calculating the weight from the height is 5 feet=100 lb., and add 8 lb. for every full inch above 5 ft.; or in men over 5 ft. 8 in., add 4 lb. for each inch. Example: 5 ft. 9 in.=100+8×6=148 lb.

CHILDREN

AGE	Boys		Girls		Boys		Girls	
	cm.	in.	cm.	in.	kg.	lb.	kg.	lb.
1 day	50	20	50	20	8.2	7	8.2	7
8 days	50	20	50	20	8.0	6½	8.0	6½
2 weeks	51	20½	51	20½	8.7	8	8.7	8
1 month	53	21	53	21	4.4	9½	4.4	9½
2 months	55	22	55	22	5.0	11	5.0	11
3 months	57	23	57	23	5.6	12½	5.6	12½
5 months	60	24	60	24	6.4	14	6.4	14
8 months	65	26	64	25½	7.5	16½	7.4	16½
10 months	67	27	67	27	8.2	18	8.2	18
12 months	70	28	70	28	9.0	19½	9.0	19½
2 years	80	32	80	32	11.5	25½	11.5	25½
4 years	96	38½	95	38	15.5	34	15.8	38½
5 years	103	41	102	41	17.5	38½	17.0	37½
6 years	109	43½	108	43	19.0	41½	18.5	40½
7 years	115	46	114	45	21.0	46½	20.0	44
8 years	120	48	120	48	22.5	49½	22.0	48½
9 years	125	50	125	50	25.0	55	24.0	52½
10 years	130	52	130	52	27.0	59½	27.0	59½
11 years	135	54	134	53½	30.0	66	29.0	63½
12 years	140	56	139	55½	32.0	70½	32.0	70½
14 years	144	57½	145	58	35.0	77	36.0	79½
14 years	148	59	150	60	38.0	83½	40.0	88
15 years	156	62½	154	61½	45.0	99	45.0	99

ANATOMICAL AND PHYSIOLOGICAL NORMALS

In examinations in the pathological or chemical laboratory the following may be considered approximately as normal findings:

ADRENALS. Length 2.4 to 2.8 in. Breadth 1.2 to 1.4 in. Weight 0.17 to 0.21 oz. each. Left usually larger.

APPENDIX. Length, quite variable, 3.5 to 4 in. Diameter 0.25 in. Weight 0.25 to 0.5 oz.

BLADDER. Capacity 16 oz. when normally distended. Thickness of wall 0.1 in. Weight 1 to 2.1 oz.

BRAIN. Weight, female 44 to 45 oz., male 48 to 51 oz. Length 6.5 in. Transverse diameter 5.5 in. Vertical diameter 5 in. Dimensions in female being 0.4 in. less.

GALL BLADDER. Length 3 to 4 in. Diameter 1 to 1.25 in. Thickness of wall 0.04 to 0.07 in. Capacity 1 to 1.5 oz.

HEART. Weight, female 8.8 to 9.8 oz., male 9.5 to 12.7 oz. Length 4.5 to 5.5 in. Breadth 3 to 4 in. Thickness 2 to 3.1 in. Thickness, wall left ventricle 0.35 to 0.47 in., right ventricle 0.1 to 0.12 in.

1712 ANATOMICAL & PHYSIOLOGICAL NORMALS

Circumference, mitral orifice 4.1 to 4.3 in. Circumference, tricuspid orifice 4.7 to 5 in. Circumference, aortic orifice 3 to 3.2 in. Circumference, pulmonary orifice 3.4 to 3.6 in.

INTESTINES. Small intestine, length 22.5 ft.; $\frac{2}{5}$ jejunum and $\frac{3}{5}$ ileum Diameter from 1.85 in. in duodenum to 1.06 in. at the end of ileum. Large intestine, length 70.9 to 76.8 in. Duodenum, length 10.2 to 11.2 in.

KIDNEYS. Weight, left 5.3 oz., right 5 oz. Thickness of cortex 0.4 in. Length 4.5 in. Breadth 2.50 in. Thickness 1.25 in. The left longer and the right thicker.

LIVER. Weight 50 to 60 oz. Greatest transverse diameter 7.9 to 9.5 in. Greatest antero-posterior diameter 3.9 to 5.9 in. Vertical diameter 5 to 6 in.

LUNGS. Weight, combined 36 to 45 oz. Weight, male right lung 24 oz., left lung 21 oz. Weight, female, right lung 17 oz., left lung 14.8 oz. Length 10 to 12 in. Antero-posterior diameter at base 7.8 in. Transverse diameter at base 4 to 5 in. The right lung is shorter, broader and thicker than the left. Dimensions in the female average 1 in. less.

MAMMARY GLAND. Weight in adult 5.25 to 7 oz. Weight during lactation 14 to 31.75 oz.

ESOPHAGUS. Length 10 to 12 in. Diameter of lumen 1.25 in. Thickness of wall 0.3 in. Weight 1.4 oz.

OVARIES. Weight 0.12 to 0.25 oz. Length 1.5 in. Breadth 0.75 in. Thickness 0.5 in.

PANCREAS. Weight, quite variable 2.1 to 4.8 oz. Length varies, averages 6 to 8 in.

PARATHYROIDS. Length 0.2 to 0.25 in. Breadth 0.15 to 0.17 in. Thickness 0.05 to 0.075 in.

PITUITARY BODY. Length 0.3 in. Breadth 0.5 in. Weight 5 to 10 gr.

PROSTATE. Weight 0.8 oz. Length 1.25 to 1.5 in. Breadth 1.5 to 1.75 in. Thickness 1 in.

SALIVARY GLANDS. Parotid, weight 0.8 to 1 oz. Sublingual, weight 0.06 to 0.09 oz. Submaxillary, weight 0.25 to 0.3 oz.

SPLEEN. Weight 5.5 to 6.9 oz. Length 4 to 5 in. Breadth 3 in. Thickness 1 to 1.5 in.

STOMACH. Capacity 1 to 2 quarts. Thickness of wall 0.25 in. Weight 4.5 to 6.2 oz.

TESTES. Weight 0.65 to 0.8 oz. each. Length 1.5 in. Breadth 1 in. Thickness 0.8 in.

THYMUS GLAND. Weight at birth 0.5 oz. and increases to 0.9 oz. at the end of second year when it gradually decreases until gland disappears. Dimensions at birth, length 2.4 in., breadth 1.5 in. and thickness 0.25 in.

THYROID. Transverse diameter 2.4 to 2.8 in. Height 1.2 in. Weight 1 to 1.4 oz.

URETHRA. Male, length 6.4 to 8.25 in.; prostatic 1 to 1.25 in.; membranous 0.6 to 1 in. and the anterior 4.75 to 6 in. Female, length 1.5 in. Diameter of lumen averages 0.25 to 0.6 in.

UTERUS (Virginal). Length 2.8 in. Breadth 1.6 in. Thickness 1 in. Weight 1.4 to 1.8 oz. The dimensions of a multiparous uterus are each increased 1 cm. or more and the weight is increased 0.7 oz. Length of cavity in virgin 2 in. in multiparae 2.25 in.

DENTITION TABLE

MILK TEETH. The first dentition begins at the sixth or seventh month, and is completed by about the second year.

Central incisors	(1) lower	6th to 8th month
"	(2) upper	7th to 9th
Lateral incisors	(1) upper	9th to 10th
"	(2) lower	10th to 13th
First molars		12th to 14th
Canines		17th to 20th
Second molars		2nd to 3rd year.

The full primary dentition is 20 teeth; 10 in each jaw.

PERMANENT TEETH. First molars, sixth year; central incisors, sixth to seventh year lateral incisors, eighth year; lower canines and first pre-molars, tenth year; upper canines and second pre-molars, eleventh year; second and third molars, from the sixteenth to twenty-fifth year.

RESPIRATION

Two months to two years	35 per minute
Two to six years	23 " "
Six to twelve years	20 " "
Twelve to fifteen years	18 " "
Fifteen to twenty-one years	16 to 18 " "

Respiration in the adult female is usually slightly more rapid than in the male, especially during pregnancy.

PULSE RATE AT VARIOUS AGES

<i>Ages</i>	<i>Beats per minute</i>
In the foetus in utero ...	Between 70 and 80
In new-born infants ...	Between 150 and 140
During first year ...	Between 140 and 130
During second year ..	From 130 down to 115
During third year ..	From 115 down to 100
From seventh to fourteenth year ...	From 105 down to 95
From fourteenth to twenty-first year ...	From 90 down to 80
From twenty-first to sixtieth year ...	Between 75 and 79
In old age ...	Between 75 and 80

The pulse is generally more frequent in females than in males; during and after exertion, unless long continued; during digestion or mental excitement; also more frequent in the morning than later in the day. It is temporarily accelerated after a sudden change of posture from the recumbent to the sitting, and from either to the standing position, especially during convalescence; and in other states where the action of the heart is feeble.

Classification of the Anæmias

Main groups	Smaller groups	Examples of clinical syndrome	Generic characters of blood picture
1. True secondary anæmia	Due to hemorrhage, external, from mucous surface, or into serous cavities		
	(A) Following external or internal injury	(A) Severed femoral or brachial artery, rupture of spleen or hemothorax	<p>The blood picture will depend on whether the condition is acute or chronic</p> <p>(A) Will in nearly every instance be acute and (D) chronic, (B) and (C) may be acute or chronic</p> <p><i>Acute</i></p> <p>Normocytic or slightly microcytic, orthochromic</p> <p>Reticulocytes ++</p> <p><i>Chronic</i></p> <p>Microcytic Hypochromic</p> <p>Reticulocytes + or +</p> <p>Erythroblasts, polychromasida, and anisocytosis</p> <p>Van den Bergh reaction negative</p> <p>No urobilin in urine</p>
	(B) Associated with disease of tissues	(B) (i) Alimentary tract from mouth to anus, e.g. (a) from teeth, from gastric, duodenal, typhoid or dysenteric ulcer, or malignant disease, or from (ii) Respiratory tract, e.g., from nose, or from lung (in phthisis) (iii) Urinary or genital tract, e.g., stone, malignant or benign new growth in kidney pelvis or bladder, ectopic gestation, bleeding into peritoneum, anti or postpartum hemorrhage or metrorrhagia (iv) Other tissues, e.g., suppurating wounds	
	(C) Associated with disease of the blood	(C) Congenital defect—hemophilia Idiopathic diseases—thrombocytopenia	
	(D) Associated with parasitic infections	(D) Hookworm and bilharzia infection with loss from intestinal and urinary tracts	

II. Errors of Erythro-
genesis

(A) Aplasia or hypoplasia of toxic or mechanical origin	(A) Aplasia or hypoplasia of toxic or mechanical origin	(A) Aplasia or hypoplasia of toxic or mechanical origin	(A) Aplasia or hypoplasia of toxic or mechanical origin
Due to—	Due to—	Due to—	Due to—
(i) Unknown causes, i.e., primary	(i) Unknown causes, i.e., primary	(i) Unknown causes, i.e., primary	(i) Unknown causes, i.e., primary
(ii) Bacterial and metabolic toxias	(ii) Bacterial and metabolic toxias	(ii) Bacterial and metabolic toxias	(ii) Bacterial and metabolic toxias
(iii) Chemical poisons	(iii) Chemical poisons	(iii) Chemical poisons	(iii) Chemical poisons
(iv) Mechanical interference with blood formation	(iv) Mechanical interference with blood formation	(iv) Mechanical interference with blood formation	(iv) Mechanical interference with blood formation
(c) Exhaustion	(c) Exhaustion	(c) Exhaustion	(c) Exhaustion
(B) Dysplasias—nutritional	(B) Dysplasias—nutritional	(B) Dysplasias—nutritional	(B) Dysplasias—nutritional
(i) Iron deficiency	(i) Iron deficiency	(i) Iron deficiency	(i) Iron deficiency
(a) Actual	(a) Actual	(a) Actual	(a) Actual
(b) Relative	(b) Relative	(b) Relative	(b) Relative
(c) Failure of absorption	(c) Failure of absorption	(c) Failure of absorption	(c) Failure of absorption
(ii) Deficiency of hemopoietic principle	(ii) Deficiency of hemopoietic principle	(ii) Deficiency of hemopoietic principle	(ii) Deficiency of hemopoietic principle
(a) Absence of intrinsic factor	(a) Absence of intrinsic factor	(a) Absence of intrinsic factor	(a) Absence of intrinsic factor
(b) Absence of extrinsic factor	(b) Absence of extrinsic factor	(b) Absence of extrinsic factor	(b) Absence of extrinsic factor
(a) Actual	(a) Actual	(a) Actual	(a) Actual
(β) Relative	(β) Relative	(β) Relative	(β) Relative
(c) Failure of absorption of combination of extrinsic and intrinsic factors, i.e., of the hemopoietic principle	(c) Failure of absorption of combination of extrinsic and intrinsic factors, i.e., of the hemopoietic principle	(c) Failure of absorption of combination of extrinsic and intrinsic factors, i.e., of the hemopoietic principle	(c) Failure of absorption of combination of extrinsic and intrinsic factors, i.e., of the hemopoietic principle

A large and varied group, but generally Normocytic
Orthochromic
Reticulocytes few
Van den Bergh—negative
No urobilin
but in all aplastic states there may be a few areas or hyperplasia in the bone marrow

Microcytic
Hypochromic
Reticulocytes ±
Urobilin — live
Van den Bergh — live
Normoblasts

Macrocytic
Hyperchromic
Urobilin +
Van den Bergh ++
Megaloblasts
Reticulocytes ±

Main groups	Smaller groups	Examples of clinical syndrome	Generic characters of blood picture
III. Errors of Erythrolysis	(iii) Deficiency of (a) Vitamin C (b) Thyroxin	(iii) (a) Anæmia of scurvy (b) Anæmia of myxedema	Microcytic Hypochromic
	(A) Conditions affecting the red cells and rendering them more susceptible to normal lytic processes	(A)	
	(i) Abnormality of red cell structure (ii) Abnormality of physical condition of red cells, e.g., increased fragility (iii) Effect of toxins, snake venoms, chemical poisons, etc. (iv) Parasitization (c) Unknown causes	(i) Sickle-celled anæmia. (ii) Acholuric jaundice, paroxysmal hemoglobinuria (iii) Anæmia associated with streptococcal and other bacterial infections, lead poisoning, novarsenobillon injections, etc. (iv) Malaria and Oroya fever (v) Acute hemolytic anæmia of Lederer	Microcytic or normocytic Orthochromic usually, occasionally slightly hyper — or hypochromic Reticulocytes ++ Urobilin +++ Van den Bergh ++ Increased fragility of red cells
	(B) Conditions causing overaction of erythrolytic tissues	(B) Splenic anæmia, and probably chronic malaria and kala-azar	As above, but decreased red cell fragility

HÆMORRHAGIC SYNDROMES

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The Hæmorrhagic Syndromes

PRIMARY HÆMORRHAGIC DIATHESSES							Secondary or Symptomatic Purpura
	HÆMORRHAGIC		ALLERGIC		HÆMOPHILIC		
	Purpura Simplex	E-sential Thrombopenia	Schonlein's Purpura	Henoch's Purpura	Hæmophilia	Hæmogenia (Female Hæmophilia)	
Characters of exudate or hemorrhage	Red cells only. Crops of spots	Whole blood, spots, ecchymoses and hemorrhages from mucous membranes after slight trauma	Serum or whole blood, spots, urticaria and localized oedemas	Serum or whole blood, scanty spots, urticaria. Effusion in to joints. Blood in stools	Whole blood. External bleeding and joint effusions	Whole blood. Spots. Ecchymoses. Hemorrhages from slight injuries	Infective, Feh- ric, Cachectic, Chemical, Mechanical
Blood							
(1) Red cor- puscles	Diminished. Reticulocytes present	Diminished Reticulocytes present	Normal	Normal	Diminished	Diminished	Icteric Avita- minotic Anæmic, etc.
(2) Platelets	Normal	Greatly reduced	Normal	Normal	Normal	Reduced in half the cases	..
(3) Coagula- tion time	Normal	Normal	Normal	Normal	Greatly prolonged	Normal	..
(4) Bleeding time	Increased	Greatly increased	Normal	Normal	Normal	Greatly increased	..
Age and sex chiefly affected	Children and young adults	Any age	Young adult males	Infants or adults	Age 2 to 20. Males only. Hereditary	Females, 2; Males 1; Hereditary	..
Prognosis	Good	Good with correct treatment; otherwise bad	Runs prolonged course	Serious	Hopeless (death before 20)	Serious. Improves in adult life	..
Therapeutic indication	Arsenic	Spinecomy (in remission stage only)	Calcium	Opium. Serum	Snake venom (vipetine). Blood transfusion restores coagulation time	Arsenic. Splenec- tomy always con- tra-indicated	..
Notes	Classified sometimes under Allergic group	...	Includes rheuma- tic purpura	..	Transmitted by females who do not suffer	Has no relation to hæmophilia and is only transmitted by actual infection	..

Typical Blood Counts of Various Blood Diseases

	Normal (average)	Idiopathic Hypo- chromic anemia and chlorosis	Pernicious anemia	Leucocytosis viz. Pneumonia	Chronic mye- loid leukæmia	Chronic lym- phoid leukæmia
Erythrocytes {	Male 5,800,000 { Female 4,800,000 }	4,850,000 (87%)	1,200,000 (24%)	4,655,000 (98%)	2,750,00 (55%)	2,500,000 (50%)
Hæmoglobin {	Male 16 gm. { Female 14 gm. }	56% (8.1 gm.)	37% (5.4 gm.)	90% (13.0 gm.)	50% (7.3 gm.)	45% (6.5 gm.)
Colour index	1	0.64	1.54	0.97 (90 t. 98%)	0.99	0.9
Leucocytes	7,000 per c. mm.	5,700	2,500	19,600	460,000	500,000
Lymphocytes	1,890 (27%)	2,508 (44%)	1,130 (45.2%)	1,960 (10%)	4,600 (1%)	495,000 (99%)
Polymorphs	4,620 (66%)	2,921 (53%)	1,837 (53.5%)	16,562 (84.5%)	184,000 (40%)	5,000 (1%)
Myelocytes	0	0	0	0	197,340 (42.9%)	0
Large mono- and transitional {	280 (4%)	28.5 (0.5%)	32.5 (1.3%)	1,078 (5.5%)	460 (0.1%)	0
Eosinophile	175 (2.5%)	114 (2%)	0	0	27,600 (6%)	0
Mast cells	85 (0.5%)	28.5 (0.5%)	0	0	46,000 (10%)	0

PHYSICAL CHARACTERISTICS OF BLOOD SERUM

	Normal	In Disease
Specific gravity	1'029 to 1'031	Lowered in nephritis with œdema, anæmia and marasmus.
Refractometer* value ...	1'343 to 1'350	Follows the protein content.
Freezing point	-0'56°C	Abnormally low in renal insufficiency and impending uræmia.

COMPOSITION OF BLOOD SERUM (per 100 c.cm.)

	Normal	In Disease
Dried residue ...	18 to 22 gm.	Diminished in nephritis with œdema, anæmia and marasmus.
Total nitrogen	1'04 to 1'2 gm.	Diminished in nephritis with œdema, anæmia and marasmus.
Protein ..	6'5 to 7'5 gm.	Diminished in nephritis with œdema, anæmia and marasmus.
Rest nitrogen ..	20 to 35 mg.	Increased in renal insufficiency and impending uræmia.
Urea ...	30 to 40 mg.	Increased in renal insufficiency and impending uræmia.
Uric acid ...	2'0 to 3'5 mg.	Increased in gout and renal insufficiency.
Creatinin ..	1'0 to 1'5 mg.	Increased in renal insufficiency.
Sugar ...	70 to 110 mg.	Increased in diabetes mellitus.
Chlorides ...	560 to 600 mg.	Increased in nephritis with œdema.
Calcium ...	9 to 11 mg.	Diminished in tetany and in severe nephritis.

WHITE BILE

White bile is sometimes found in the biliary tract when its contents have been dammed up by some obstruction. This secretion may be found, according to the actual site of the obstruction in the dilated gall bladder or in the dilated biliary ducts where these have been isolated from the gall-bladder. In every case bile salts and pigment were entirely absent; cholesterol was present only in small amounts, if at all; chlorides were present in approximately the same concentration as in the blood serum. Calcium was found in amounts corresponding with the blood levels. (*Med. Jour. Australia*, Vol. 1, No. 3, 1935).

ABNORMAL BLOOD CELLS IN THE PERIPHERAL CIRCULATION

Cells	Cytoplasm	Nucleus	REMARKS
Adult megalo- blasts (10 to 12 μ)	Deeply basophilic	Large. Occupies most of the cells. Stains lightly. Delicate threads of chromatin often with nucleoli	Cell outline often irregular very few present in normal marrow
Erythroblasts (8 to 10 μ)	Early forms : basophilic. Late forms : polychromatic	Smaller than that of megalo blasts. Chromatin less reticulate and more deeply stained. May be cart wheel	
Normoblast (6 to 8 μ)	Polychromatic or eosinophilic (orthochromatic)	Dense chromatin deeply stained. Sometimes eccentric	Nucleus may be lobed or clover leaf
Embryonic hæmoglobinised megalo blast (Ehrlich) (10 to 14 μ)	Polychromatic or eosinophilic	Large clear and reticular but often much more mature	Large cells are known as giganto blasts. Very mature forms may have pyknotic nucleus

COLLECTION OF BLOOD FOR DIFFERENT EXAMINATIONS

No preparation is usually necessary except that the blood for special cases should be drawn in the morning before the patient takes any food, it is essential, however, that the specimen is properly labelled and sent to the laboratory immediately after collection.

The following table gives an idea of the approximate quantity of blood required and the method of collection.

Examination or estimation of :	Quantity of blood. in c.cm.	To be collected in :
Sugar ...	2	Oxalated tube
Urea ...	2	" "
Non-protein nitrogen ...	5	" "
Cholesterol ...	3	" "
Calcium (in serum) ...	3	Sterile test tube
Van den Bergh's test ...	5	" " "
Aldehyde test ...	2	" " "
Antimony test ...	2	" " "
Widal reaction ...	2	" " "
W. R. ...	3	Clean phial
Culture ...	5-10	Broth tube
Grouping ..	5	{ 2 c.cm. in citrated tube { 3 c.cm. in test tube

OBSTETRIC TABLE

The calculation is made from the first day of the last menstrual period

January October	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	January November
February November	8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	February December
March December	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	March January
April January	6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	April February
May February	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	May March
June March	5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	June April
July April	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	July May
August May	7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	August June
September June	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	September July
October July	8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	October August
November August	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	November September
December September	8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	December October

PRINCIPAL HILL STATIONS AND HEALTH RESORTS IN INDIA

Almora (United Provinces). Altitude 5,200 to 5,500 ft. District headquarters with contonment; six hours journey by car from Kathgodam, the terminus of R. & K. Ry.; situated on saddle shaped, bare ridge. Little vegetation, rocky soil, good natural drainage. Well reputed all over India as a resort for cases of tuberculosis of lungs; with leper asylum. Rainfall 42.55 in. Season—April to October.

Bangalore (Mysore State). Altitude 3,021 ft. Seat of Government of Mysore State and headquarters of Bangalore Brigade of Indian Army. A lively specimen of Hindu town. Climate noted for its salubrity, pleasant, cool, congenial for convalescents; wettest months generally September and October. Rainfall 36.57 in.; annual normal relative humidity 78 per cent.; annual normal maximum 84.5°F. and minimum 64.2°F.

Coomoor (Madras). Altitude 6,000 ft. At the south corner of Nilgiri plateau and 10 miles from Ootacamund on Nilgiri Railway. The Pasteur Institute of Southern India; one of the principal sanatoria of the Presidency and perhaps second only to Ootacamund in natural advantages, built on one of the loveliest sites in India. Flowers, fruits, and vegetables grow in profusion all the year round. Possesses cool and equable climate; rainfall 66.56 in., well distributed throughout the year but heaviest during the north-east monsoon; annual mean temperature 60°F with an extreme variation not exceeding 15° either way.

Cox's Bazaar (Bengal). Subdivision in Chittagong district; well known health resort. Surrounding country hilly and very picturesque, with good game; excellent sea-bathing obtainable on fine sandy beach. Rainfall 145.77 in.; annual normal relative humidity 86 per cent.; annual normal maximum 84.9°F. and minimum 69.6°F.

Dalhousie (Punjab). Altitude 7,687 ft. In district Gurdaspur, 51 miles by road from Pathankot on N. W. Ry. Scenery compares favourably with that of any hill station in Himalayan range; very pretty, moderately sized hill station with Chamba only two stages beyond; hills consist of rugged granite. Rainfall 83.38 in. Season—May to October.

Darjeeling (Bengal). Altitude 6,000 to 7,800 ft. Summer headquarters of Bengal Government, served by D. H. Ry. Queen of Indian hill stations, picturesquely situated on a long narrow ridge, with magnificent views of snows from the observatory hill and abundant vegetation. Has well equipped sanatoria, several good educational institutions. Rainfall 123.27 in., principally from June to September when the climate is very damp, but very little during cold months; annual normal relative humidity 85 per cent.; annual normal maximum 59.3°F. and minimum 47.7°F. Best time before or after rains.

Dehra Dun (United Provinces). Altitude 2,233 ft. Cold season district headquarters, on main road from plains to hill station of Mussoorie. Pretty station with large number of retired Europeans and Anglo-Indians; headquarters of Trigonometrical Survey of India; with Forest Research Institute, Military College and a Public School. Soil rocky. Rainfall 83.16 in., abundant during monsoons; annual normal relative humidity 70 per cent.; extremes of heat and cold unknown. Season—October to March.

Dharamsala (Punjab). 16 miles north-east of Kangra in the midst of wild and picturesque scenery; with beautiful waterfalls within a short distance at Bhagsu Nath; well wooded with oaks and other forest trees. Rainfall 115.75 in., atmosphere peculiarly damp during 3 months of rainy season.

Gulmarg (Kashmir). Altitude 8,500 ft. One of the loveliest and most enjoyable hill stations in India, 28 miles from Srinagar; famous for golf course; plenty of picnic spots in the neighbourhood. Accommodation in well furnished, electrically lighted wooden huts mostly owned by the State, or in hotels both European and Indian. Season—June to middle of September.

Hazaribagh (Bihar). Altitude 2,000 ft. District headquarters; picturesquely situated on high central plateau of district in the midst of conical hills, with many fine lakes in the vicinity; motorable roads in and outside the town. Temperature moderate except during hot months of April to June. Rainfall 52.73 in.; annual normal relative humidity 63 per cent.; annual normal maximum 84.6°F. and minimum 65.7°F.

Kalimpong (Bengal). Altitude 4,200 ft. Headquarters of subdivision in Darjeeling district, 28 miles by road from Darjeeling or 12 miles from Giele Kholā the D. I. Ry. terminus. Commands beautiful view of mountain, valley, and river scenery; has well equipped Charteris hospital, also St. Andrews Colonial Homes for education and training of poor European and Eurasian children. There is a proposal to start tuberculosis sanatorium here. Climate milder than Darjeeling. Rainfall 88.34 in.; annual normal relative humidity 84 per cent.; annual normal maximum 69.5°F. and minimum 57.6°F.

Karachi (Sind). Rapidly developing sea-port at extreme end of Indus delta, with modern architecture. Climate, owing to prevalence of sea breezes during 8 months, more healthy than at any other place in Sind; hottest months April to June. Rainfall about 5 in.; annual normal relative humidity 72 per cent.; annual normal maximum 93.4°F. and minimum 68.2°F.

Kasauli (Punjab). Altitude 6,335 ft. Cantonment and convalescent depot in Ambala district; situated on the crest of the hill overlooking Kalka valley, 9 miles by bridle path and 15 miles by motor road from Kalka on N. W. Ry.; good natural drainage; Pasture Institute of India. Rainfall 61.02 in. Season—April to October.

Kodaikanal (Madras). Altitude 7,688 ft. One of the largest sanatoria in the Presidency. On a plateau of the Palney hills, a spur of Ghats, in Madura district. Reached via Kodaikanal Road station on South Indian Railway. Much resorted to by Europeans throughout the year; temperature somewhat milder than Ootacamund. Rainfall lighter and atmospheric conditions more equable than those of Nilgiris; climate of the place one of the best in India. Round about are rolling downs, with beautiful little woods nestling in their hollows and perennial streams flowing through them; lake provides fine boating and fishing; noted for its dry gravelly soil. Rainfall 63.94 in.; annual normal relative humidity 69 per cent.; annual normal maximum 64.6°F. and minimum 51.1°F.

Lansdowne (United Provinces). Altitude 5,500 to 6,600 ft. Cantonment in Garhwal district, about half way between Mussoorie and Nainital; extends through beautiful pine and oak forests for more than 3 miles. Rainfall 78.98 in.

Mahabaleshwar (Bombay). Altitude 4,500 to 4,700 ft. Principal sanatorium of Bombay Presidency in Satara District; 39 miles from Wathar on Southern Mahratta Railway. Picturesque scenery and proximity to fresh sea breeze; spring and autumn retreat of Bombay Governor and officials; favourite season March to June, but this is not the time when it is most beautiful; in October, on cessation of monsoon, it is full of flowers and verdure; excellent drives and walks in all directions. Monsoon sets early June and worst in July. Rainfall 265.6 in.

Maymyo (Burma). Altitude 3,545 ft. Principal hill station in Burma, district Mandalay, on Mandalay Lashio Railway; occupies un-

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dulating plateau surrounded by hills covered with thin oak forests and bracken; enjoys temperate and on the whole salubrious climate. Rainfall 58.62 in., heaviest in May, June, September, and October; annual normal relative humidity 86 per cent.; annual normal maximum 76.6°F. and minimum 56.4°F.

Mount Abu (Rajputana). Altitude 3,945 ft. Eighteen miles from Abu Road on B. B. & C. I. Ry.; sanatorium and celebrated place of pilgrimage. Climate very healthy and delightfully cool. Polo, golf, cricket, and boating, etc., available. Rainfall 61.80 in.; annual normal relative humidity 54 per cent., annual normal maximum 75.9°F. and minimum 62.0°F.

Murree (Punjab). Altitude 7,507 ft. Hill sanatorium and headquarters of tahsil in Rawalpindi district, 89 miles from Rawalpindi on N. W. Ry.; commands magnificent view over forest-clad hill sides into deep valleys studded with villages and cultivated fields; admirable climate, suitable for children; sanatorium for tuberculosis of lungs recently started; has Lady Roberts Home for invalid officers and Murree Brewery. Rainfall 56.90 in.; annual normal relative humidity 56 per cent.; annual normal maximum 65.1°F. and minimum 50.2°F. Season—April to October.

Mussoorie (United Provinces). Altitude 6,000 to 7,500 ft. Hill station and sanatorium in Dehra Dun District, among beautiful and varied mountain scenery; two hours drive from Dehra Dun, important as an educational centre for European children; many excellent hotels and nursing homes; massage and electric treatment available. Rainfall 93.84 in.; annual normal relative humidity 65 per cent.; mean temperature 57.1°F.

Nainital (United Provinces). Altitude 6,400 ft. Summer headquarters of the Government of United Provinces, with contourment; 21 miles from Kathgodam the R. K. Ry. terminus. Cup-shaped station with pear-shaped lake in the middle, a little more than 2 miles in circumference, with good boating arrangements, unless accommodation obtained near top, it cannot be said to be healthy. Ramsay Hospital for Europeans with large maternity block. Rainfall 97.94 in. Season—April to October.

Ootacamund (Madras). Altitude 7,327 ft. Headquarters of Nilgiri district and summer seat of Madras Government, chief sanatorium of the Presidency and one of the most beautiful hill stations in India; standing on the Nilgiri plateau, Nilgiri Railway. Station reposes in an amphitheatre surrounded by 4 hills; flowers blossom in profusion all the year round. Rainfall 52.14 in.; annual normal relative humidity 68 per cent.; annual normal maximum 65.5°F. and minimum 49.2°F.

Pachmarhi (Central Provinces). Altitude 3,528 ft. Sanatorium in Hoshangabad district, summer resort of C. P. Government; 32 miles from Pipariya station on G. I. P. Ry. Stands on plateau of Satpura hills, forest growth generally thin, interspersed with numerous grass glades of park-like appearance; affords slight relief from heat of plains, May the hottest month but not oppressive; climate delightfully cool and bracing in second half of September and October. Rainfall 76.89 in., heaviest in June to September; annual normal relative humidity 60 per cent.; annual normal maximum 79.8°F. and minimum 61.0°F.

Pahalgam (Kashmir). Altitude 7,200 ft. Sixty miles from Srinagar by motor road; admirably situated beside Lidder tributary of Jhelum river, coniferous forests all round, drinking water from several good springs. Climate salubrious, cool, congenial for convalescents, less rainy than Gulmarg. Much resorted to by Indians; accommodation chiefly in tents available locally on moderate charges. Season—June to September.

Parachinar (North West Frontier Province). Headquarters of Kurum Agency. Three hours drive from Thal station on N. W. Ry.; in the midst of wide open valley encircled by hills. Climate cold—except in mid-summer—and dry, very healthy, suitable for convalescents. Some of the best varieties of fruits available. Rainfall 28.39 in.; annual normal relative humidity 55 per cent.; annual normal maximum 70.1°F. and minimum 48.0°F. Season—May to October.

Puri (Orissa). Headquarters of Puri district; popular health resort with good sea-bathing, on B. N. Ry., celebrated for Jagannath temple; has several hotels. The site is salubrious and monsoon blows fresh and cool from sea, less healthy during rains. Rainfall 53.99 in.; annual normal relative humidity 83 per cent.; annual normal maximum 86.3°F. and minimum 74.6°F.

Quetta (Baluchistan). Altitude 5,502 ft. Capital of Baluchistan and important military station on N. W. Ry., now in ruins on account of the 1935 earthquake; has severe winter and suffers from blizzards, dust-storms frequent in summer; well-known for fruits, has fine turfed polo and cricket grounds. Rainfall 9.37 in.; annual normal relative humidity 58 per cent.; annual normal maximum 73.6°F. and minimum 44.3°F.

Ranchi (Bihar). Altitude 2,128 ft. Summer seat of Bihar Government; situated on Chota Nagpur plateau on B. N. Ry. Much used by Europeans as health resort in cold-weather months; has mental hospitals for Indians and Europeans. Rainfall 54.72 in.; annual normal relative humidity 66 per cent.; annual normal maximum 84.2°F. and minimum 65.5°F.

Ranikhet (United Provinces). Altitude 5,983 to 6,942 ft. Military sanatorium in Almora district, 52 miles from Kathgodam by motor; more or less on flat so that horse conveyances and motors can be used; has a good golf course and extensive pine woods. Rainfall 52.13 in.; annual normal relative humidity 67 per cent.; mean temperature 60.3°F. Season—April to October.

Shillong (Assam). Altitude 4,920 ft. Headquarters of Assam Government; 67 miles by road from Gauhati on Assam Bengal Railway, situated on a plateau in Khasia Hills. Town laid out with great judgment and taste among pine woods, surrounded with rolling downs; visitors can enjoy riding, driving, polo, golf, and cricket; excellent climate, temperature more equable than that of any hill station in India, seldom above 80°F. in hottest weather. Rainfall 81.08 in.; annual normal relative humidity 74 per cent.; annual normal maximum 69.9°F. and minimum 53.4°F.

Simla (Punjab). Altitude 7,232 ft. Summer Headquarters of Governments of India and the Punjab; on N. W. Ry., Nalka-Simla section. Ripon hospital for Indians and Walker for Europeans; electric treatment obtainable; some near localities recommended for invalids; several excellent hotels. Rainfall 63.07 in.; annual normal relative humidity 57 per cent.; annual normal maximum 60.9°F. and minimum 49.7°F. Season—April or May to October.

Srinagar (Kashmir). Altitude 5,204 ft. Capital of Kashmir State; 196 miles from Rawalpindi or about similar distance from Jammu on N. W. Ry.; admirably situated on banks of navigable river Jhelum, with lovely Moghul gardens in the neighbourhood; accommodation principally in well furnished, electrically lighted house boats. Rather warm during June to August, but cooler places within easy reach; winter months very sunless. Has Cottage Hospital for the Europeans and large Mission Hospital for Indians. Rainfall 25.73 in.; annual normal relative humidity 82 per cent.; annual normal maximum 66.1°F. and minimum 44.1°F. Season—April to June, and September to November.

1726 CLASSIFICATION OF MINERAL WATERS

CLASSIFICATION OF MINERAL WATERS

The mineral waters available in the Western Countries are classified below according to their constituents. The mineral waters and springs found in India are also grouped in a tabular form for convenience.

Class	Spa	Characteristics
(1) Thermal Radio active of Low Mineralisation	... Buxton	... Warm, 82°
	... Bath	... Hot, 104° to 120°
	... Wildbad	... 91° to 105°
	... Plombières	... 77° to 155°, arsenical
	... Aix-les-Bains	... 109° to 122°, H ₂ S
(2) Muriated : Simple	Droitwich	} Hypertonic, 30 per cent. NaCl, external use only
	Nantwich	
	Woodhall Spa	... Contains Br and I
	Langammarch	... Contains barium
	Wiesbaden	... Isotonic or hypotonic
Alkaline	... Cheltenham (Pittville)	... Internal use
	... Ems	... 116°, CO ₂
	... Royat	... 95°, CO ₂
	... Hamburg	...
	... Nauheim	... Hot effervescing
	... Kissingen	...
Sulphated	... Cheltenham	... Internal use
	... Leamington	... Internal use
Alkaline	... Karlsbad	... Hot, internal use
Sulphated	... Marienbad	... Cold, internal use
(3) Sulphated (pure)	Apenta	} Bottled
	Rubinät	
	Hunyadi Janos	
(4) Alkaline : Carbonated	... Vichy	...
(5) Sulphur : Simple	Strathpeffer	...
	Isanwryd Wells	...
Muriated	... Harrogate	...
	... Landrindod	...
	... Helouan	... Hot
	... Rotoura	... Hot
	... Aachen	...
(6) Arsenical	... Levico	... Bottled
	... Mont Dore	... Low mineralisation
	... La Bourboule	... Muriated
(7) Calcareous	... Bath	... Hot
	... Contrexeville	... Cold
	... Wildungen	...

(8) Chalybeate :				
Ferrous	car-			
bonate	...	Strathpeffer	...	
		Buxton	...	
		Harrogate	...	
		Tunbridge Wells	...	
		Spa	...	CO ₂ , effervescent
Ferrous	sul-			
phate	Muriat-	Trefriw	...	
ed. FeCl	...	Harrogate	...	

MINERAL WATERS IN INDIA

Places	Temperature of the water	Characteristics
ASSAM.		
Cachar :— <i>Kopili</i> ...	128° to 130°F	Strongly saline.
Sibsagar :— <i>Namboo</i> ...	95° to 98°F	Water slightly sulphurous. Gas slightly sulphuretted.
BALUCHISTAN.		
Bolan Pass :— <i>Kirtla</i>	Hot sulphurous.
Las Bela :— <i>Kan Berar</i>	Strongly sulphurous.
Kachhi :— <i>Lakha</i>	Intensely saline and sulphurous.
Sibi :— <i>Khattan</i> ...	109°F	Sulphurous.
BENGAL.		
Birbhum :— <i>Tanti para</i> ..	128° to 162°F	Sulphuretted hydrogen.
Chittagong :— <i>Babu or Bharat-Khund</i>	Sulphurous and chalybeate.
<i>Bakwa-Khund</i>	Diuretic and aperient.
<i>Kauri-Khund</i> ...	very hot	Saline, sulphurous and chalybeate.
<i>Brahma-Khund</i>	Saline, slightly chalybeate.
Darjeeling :— <i>Mechi</i>	Carbonated, sulphurous and chalybeate.
Jessore :— <i>Khajura</i> ..	82°F	Carbonate of lime and magnesia with a small proportion of iron.
BEHAR AND ORISSA.		
Atymallik :— <i>Deolhari</i> ...	134°F	Slightly saline and sulphuretted hydrogen.
Cuttack :— <i>Atari</i> ...	138°F	Quantity of sulphuretted hydrogen.
** Hazaribagh :— <i>Belkapi or Surja-Khund</i> ...		
	169°, 170°, 190°F	Chloride and sulphate of soda

<i>Doari</i> ...	110° to 115°F	Sulphurous and slightly saline
<i>Indra jurba</i> ...	Tepid	Sulphurous.
<i>Katkamsandi</i> ...	110°F	Sulphuretted hydrogen, silica, alkaline chlorides, sulphate and iron.

Mambhum :—

<i>Tatlul or Tantolya</i>	190°F	Sulphurous and slightly clayey beate.
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Monghyr :—

<i>Bhimband</i> ...	145° to 150°F	Limpid and tasteless.
<i>Lachmi-Khund</i> ...	144°F	Not sulphurous.
<i>Panchbhur</i> ...	85.4°F	Not sulphurous.
<i>Sita Khund</i> ...	140°F	Slight odour of sulphuretted hydrogen.

Palamau :—*Jarum*

<i>Thatha</i> ...	132°F	Sulphuretted hydrogen.
	151°F	Slightly impregnated with sulphuretted hydrogen.

Patna :—*Rajghir*

Santhal-Parganas :—	100° to 110°F	Water clear and tasteless.
<i>Baramasia</i> ...	93°F	Not sulphurous.
<i>Dumka</i> ...	82°F	Not sulphurous.
<i>Jhariya or Jherwa</i>		
<i>Pani</i> ...	93°F	Not sulphurous.
<i>Sibpur</i> ...	122°F	Profuse discharge of gas slightly sulphuretted.
<i>Nunbil</i> ..	119.5°F	Sulphuretted gas.
<i>Tatloi</i> ...	148°F	Slightly sulphurous.

BOMBAY.

Kaira :— <i>Lasundara</i> ...	100° to 122°F	Strongly sulphurous and saline.
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Panch Mahals :—

<i>Tuwa or Tul</i> ...	Near boiling point	
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Ratnagiri :— <i>Arauli</i> .	105°F	Sulphurous vapour. Strongly impregnated with sulphur.
<i>Rajpur</i> ...	90°F	Alkaline. Traces of common salt and sulphate of lime.
<i>Sangameswar</i> ...	105°F	Slightly sulphurous.
<i>Rafivall</i> .	110°F	Slightly sulphurous.
<i>Manga</i> ...	99° to 117°F	Chalybeate when fresh and sulphurous on issuing.

Surat :—

<i>Anaral</i> ...	115° to 120°F	Sulphurous gas.
<i>Vizrabhi</i> ...	110° to 136°F	Sulphuretted hydrogen.

CENTRAL PROVINCES.

Chhindwara :—

<i>Anhoni</i> ...	134°F	Strongly sulphurous.
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Hoshangabad :—

<i>Anhoni Samoni</i> ...	114°F	Abundant discharge of sulphuretted hydrogen.
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Surguja :—

<i>Talapant</i> ...	130° to 190°F	Strong odour of sulphuretted hydrogen.
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KASHMIR.

Baltistan :—

<i>Asholt</i>	...	104.5°F	Sulphuretted hydrogen.
<i>Bistlo Behitsil</i>	..	160°F	Sulphuretted hydrogen.
<i>Duchin</i>	...	154°F	Slightly chalybeate.
<i>Khorkan</i>	...	185°F	Sulphurous.

Changchengmo :—

<i>Gokra</i>	...	120° to 150°F	Carbonic acid gas.
<i>Pampun</i>	...	70°F	Sulphuretted hydrogen.

Nubar :—

<i>Chausan</i>	..	167°F	Faintly sulphurous.
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Rupshu :—

<i>Puga</i>	...	80° to 174°F	Sodium chloride and sulphuretted hydrogen.
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MADRAS.

Godavari :—

<i>Gondala</i>	..	140°F	Slight odour of sulphuretted hydrogen.
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PUNJAB.

Gurgaon :—

<i>Sohna</i>	...	108°F	Strongly sulphuretted.
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Kufra :—*Bashisht*

<i>Khclat</i>	...	138°F	Sulphuretted hydrogen.
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<i>Manikara</i>	...	104°F	Sulphurous
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Spiti :—

<i>Changhtzang</i>	...	106.5° to 202°F	Sulphuretted hydrogen.
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Mianwali :—

<i>Bakh Ravine</i>	...	117.5°F	Sulphuretted hydrogen.
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Simla Hill States :—

<i>Jaori</i>	...	94°F	Sulphuretted hydrogen.
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Bhajji :—*Sunl*

	...	130.5°F	Sulphurous and Saline
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	...	135°F	Strongly sulphurous.
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RAJPUTANA.

Mewar (Udaipur)

<i>Gangar</i>	...	80°F	Slightly saline and sulphurous.
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SIKKIM.

<i>Momai</i>	..	110° to 116°F	Strongly sulphurous.
<i>Yeumtong</i>	..	112.6°F	Sulphuretted hydrogen.
			Chloride and sulphate of soda.

UNITED PROVINCES.

<i>Sahasradhara</i>	...	72°F	Strongly impregnated with sulphuretted hydrogen.
<i>Gauri Khund</i>	..	130°F	Carbonate of lime and iron.
<i>Gauri Khund</i>	...	72°F	Saline and strongly chalybeate.

NOTIFIABLE DISEASES

The following is a list of notifiable diseases in America, Great Britain, Ireland, India (Br.), and French and Portuguese territories in India.

Actinomycosis (A.)	Miliary fever (A., Fr. I.)
Adinitis, acute infectious (A.)	Mumps (A., I.)
Ankylostomiasis (A.)	Paragonimiasis (A.)
Anthrax (A.)	Paratyphoid (A., Fr. I., G.B. & Ir.)
Beri-beri (A.)	Pediculosis (A.)
Bilharziasis (A.)	Pellagra (A.)
Black-water fever (A.)	Pemphigus (A.)
Broncho-pneumonia (A.)	Pemphigus neonatorum (E. & W.)
Cancer (A.)	Plague*
Chancre, soft (A.)	Pneumonia (A., Fr. I., Sc.)
Chicken-pox (A., G.B., Ir., I.)	Poliomyelitis (A., G.B. & Ir.)
Cholera *	Psittacosis (A.)
Coccidiodal Granuloma, infectious (A.)	Puerperal fever (Sepsis) *
Continued fever (A., G.B., Ir.)	Rabies (A., E. & W.)
Dengue (A.)	Rat-bite fever (A.)
Diarrhoea and Enteritis (A., I., Ir.)	Relapsing fever *
Diphtheria and croup.*	Rheumatic fever (A.)
Distomiasis (A.)	Ring worm (A.)
Dysentery, Amoebic (A., Fr. I.)	Rocky mountain spotted fever (A.)
" Bacillary (A., Fr. I.)	Rubeola (A., E. & W.)
" unspecified (A.)	Scabies (A.)
Echinococcus infection (A.)	Scarlet fever *
Encephalitis, Epidemic lethargic (A., G.B. & Ir.)	Scurvy (A.)
Erysipelas (A., G.B. & Ir.)	Septic sore throat (A.)
Favus (A.)	Small-pox *
Filariasis (A.)	Syphilis (A.)
Food poisoning (A.)	Tetanus including infantile A., Sc.)
Foot and Mouth Disease (A.)	Tick fever (A.)
Glanders (A., E. & W.)	Trachoma (A., Sc.)
Goitre (A.)	Trench fever (Ir.)
Gonorrhoea including ophthalmia neonatorum (A.)	Trench mouth (A.)
Impetigo contagiosa (A.)	Trichinosis (A.)
Influenza *	Trypanosomiasis (A., Fr. I.)
Jaundice, infectious (A., Sc.)	Tuberculosis, pulmonary *
Leishmaniasis (A., I.)	Tuberculosis, nonpulmonary *
Leprosy (A., I., Fr. I., Pr. I.)	Tularæmia (A.)
Malaria (A., G.B. & Ir.)	Typhoid *
Malignant cedema (A.)	Typhus fever (Exanthematic) *
Measles (A., Fr. I., G.B. & Ir.)	Typhus, Benign Epidemic (A.)
Meningitis, epidemic cerebro-spinal *	Undulant fever (A., Fr. I.)
	Vincent's Angina (A.)
	Whooping cough *
	Yellow fever (A., I., Ir.)
	Yaws (A.)

* America, Great Britain, Ireland, India (Br.), and French and Portuguese settlements in India.

A.—America
E. & W.—England and Wales
Sc.—Scotland
Fr. I.—French territories in India
G. B.—Great Britain

Ir.—Ireland
I.—India (Br.)
Pr. I.—Portuguese territories in India

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